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# Annals of Surgery

41

A Monthly Review of
Surgical Science and Practice
since 1885

17 92
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Philadelphia

# Cefotan arithmetic.

+ **more cost-effective than cefoxitin**[1,2]

− **less frequent dosing than cefoxitin**[3,4]

× **several times the half-life of cefoxitin**[5,6]

÷ **single-dose prophylaxis/ twice-daily treatment**

Count on
**CEFOTAN® IM/IV**
(cefotetan disodium)
**In intra-abdominal and gynecologic infection due to indicated organisms**

References: 1. Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. 2. Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. 3. CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. 4. *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. 5. Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. 6. Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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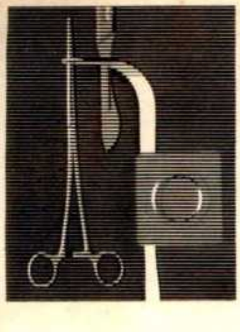

# Count on

# CEFOTAN® IM/IV

# (cefotetan disodium)

## In intra-abdominal and gynecologic infection due to indicated organisms

**For Intravenous or Intramuscular Use**
**BRIEF SUMMARY**

**INDICATIONS AND USAGE**

**TREATMENT:** CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

**Urinary tract infections** caused by *E coli*, *Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris*, *Providencia rettgeri*, and *Morganella morganii*).

**Lower respiratory tract infections** caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.

**Skin and skin structure infections** caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.

**Gynecologic infections** caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis*, *Streptococcus* species (excluding enterococci), *E coli*, *Proteus mirabilis*, *Neisseria gonorrhoeae*, *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

**Intra-abdominal infections** caused by *E coli*, *Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis*, *B ovatus*, *B thetaiotaomicron*).

**Bone and joint infections** caused by *Staphylococcus aureus*.*

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

**NOTE:** If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

**PROPHYLAXIS:** The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

**CONTRAINDICATIONS**

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

**WARNINGS**

**Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.**

**Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.**

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.

**PRECAUTIONS**

**GENERAL:** As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

**INFORMATION FOR PATIENTS:** As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

**DRUG INTERACTIONS:** Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

**DRUG/LABORATORY TEST INTERACTIONS:** A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

**CEFOTAN® (cefotetan disodium)**

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

**USAGE IN PREGNANCY: Pregnancy Category B:** Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**USAGE IN NURSING MOTHERS:** Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

**PEDIATRIC USE:** Safety and effectiveness in children have not been established.

**ADVERSE REACTIONS**

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.

**Gastrointestinal** symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

**Hematologic** laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

**Hepatic** enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

**Hypersensitivity** reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).

**Local** effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

**DOSAGE AND ADMINISTRATION**

**TREATMENT:** The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

**GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN**

| Type of Infection | Daily Dose | Frequency and Route |
|---|---|---|
| Urinary Tract | 1-4 grams | 500 mg every 12 hours IV or IM<br>1 or 2 g every 24 hours IV or IM<br>1 or 2 g every 12 hours IV or IM |
| Other Sites | 2-4 grams | 1 or 2 g every 12 hours IV or IM |
| Severe | 4 grams | 2 g every 12 hours IV |
| Life-Threatening | 6* grams | 3 g every 12 hours IV |

*Maximum daily dosage should not exceed 6 grams.

**PROPHYLAXIS:** To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

**IMPAIRED RENAL FUNCTION:** When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

**DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

| Creatinine Clearance mL/min | Dose | Frequency |
|---|---|---|
| >30 | Usual Recommended Dosage* | Every 12 hours |
| 10-30 | Usual Recommended Dosage* | Every 24 hours |
| <10 | Usual Recommended Dosage* | Every 48 hours |

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:} \quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

**HOW SUPPLIED**

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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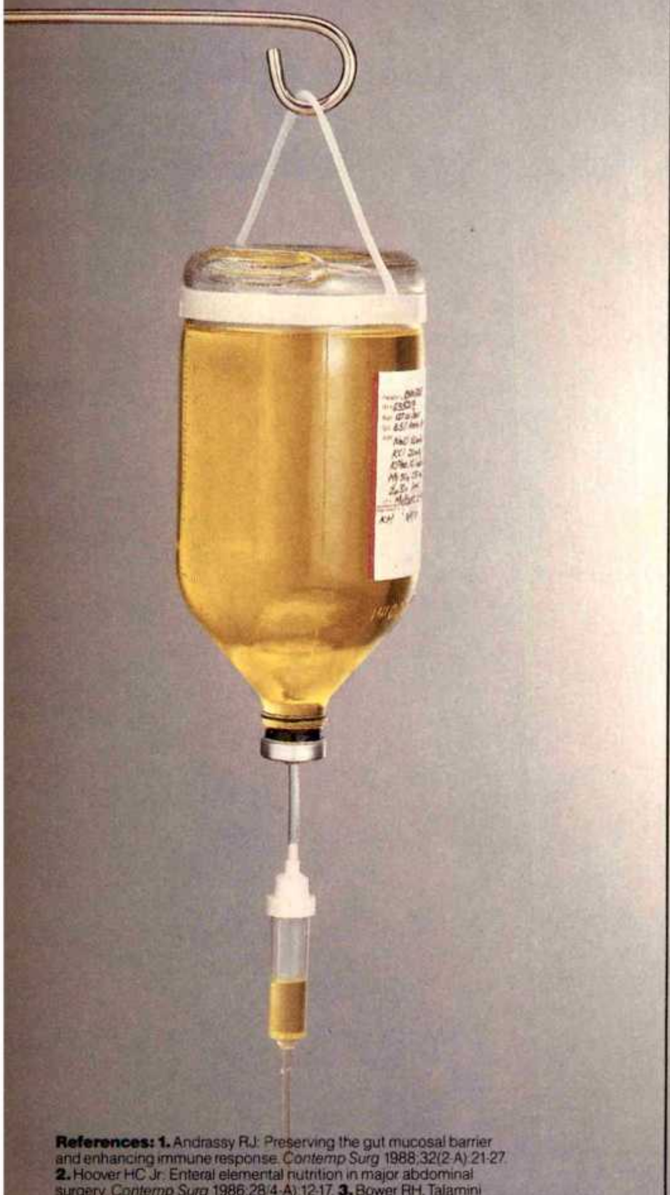

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**References: 1.** Andrassy RJ: Preserving the gut mucosal barrier and enhancing immune response. *Contemp Surg* 1988;32(2-A):21-27. **2.** Hoover HC Jr: Enteral elemental nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. **3.** Bower RH, Talamini MA, Sax HC, et al: Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045. **4.** Souba WW, Smith RJ, Wilmore DW: Glutamine metabolism by the intestinal tract. *JPEN* 1985;9:608-617. **5.** Fox AD, Kripke SA, Berman JR, et al: Reduction of the severity of enterocolitis by glutamine-supplemented enteral diets. *Surgical Forum* 1987;38:43-44. **6.** Hwang TL, O'Dwyer ST, Smith RJ: Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1986;37:56-57.

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**Vol. 213 No. 1**

# Annals of Surgery

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*John L. Cameron, M.D., F.A.C.S., and Thomas R. Gadacz, M.D., F.A.C.S.*
*Baltimore, Maryland*

### *WHAT'S NEW IN GENERAL SURGERY*

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One hundred patients undergoing laparoscopic cholecystectomy were reviewed prospectively. The technique is described in detail. A major complication rate of 4% with one bile duct injury compares favorably with open cholecystectomy. Although there are many unanswered questions with respect to laparoscopic cholecystectomy, it can be a safe technique that represents a significant advance in the management of gallstone disease.

*Jeffrey H. Peters, M.D., E. Christopher Ellison, M.D., Jeffrey T. Innes, M.D., Jonathan L. Liss, B.A., Keith E. Nichols, M.D., Jack M. Lomano, M.D., Sheri R. Roby, P.A., Mary E. Front, R.N., and Larry C. Carey, M.D.*
*Columbus, Ohio*

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*Karl H. Fuchs, M.D., Tom R. DeMeester, M.D., Ronald A. Hinder, M.D., Hubert J. Stein, M.D., Antony P. Barlow, F.R.C.S., and Naresh C. Gupta, M.D.*
*Omaha, Nebraska*

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*Charles B. Rosen, M.D., David M. Nagorney, M.D., Russell H. Wiesner, M.D., Robert J. Coffey, Jr., M.D., and Nicholas F. LaRusso, M.D.*
*Rochester, Minnesota*

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*Kenneth C. H. Fearon, M.D., Donald C. McMillan, Thomas Preston, PH.D., F. Peter Winstanley, PH.D., Anne M. Cruickshank, M.B., CH.B., and Alan Shenkin, PH.D.*
*Glasgow and East Kilbride, United Kingdom*

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*Mauro Ribeiro, M.D., Adrian J. Greenstein, M.D., Yasunobu Yamazaki, M.D., and Arthur H. Aufses, Jr., M.D.*
*New York, New York*

**Risks of Intestinal Anastomoses in Crohn's Disease** ........................................ **37**

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*Stefan Post, M.D., Michael Betzler, M.D., F.A.C.S., Bodo von Ditfurth, M.D., Guido Schürmann, M.D., Peter Küppers, M.D., and Christian Herfarth, M.D., F.A.C.S.*
*Heidelberg, Federal Republic of Germany*

**A Clinical Pilot Study Combining Surgery with Intraoperative Pelvic Hyperthermochemotherapy to Prevent the Local Recurrence of Rectal Cancer** .............. **43**

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*Shigeru Fujimoto, M.D., Makoto Takahashi, M.D., Fumio Endoh, M.D., Ram Dhoj Shrestha, M.D., Masashi Kokubun, M.D., Mitsuru Takai, M.D., and Katsuji Okui, M.D.*
*Chiba and Matsudo, Japan*

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*Ronald W. Busuttil, M.D., PH.D., Philip Seu, M.D., J. Michael Millis, M.D., Kim M. Olthoff, M.D., Jonathan R. Hiatt, M.D., Allen Milewicz, M.D., Barbara Nuesse, R.N., George El-Khoury, M.D., David Raybould, M.D., Anthony Nyerges, M.D., Jorge Vargas, M.D., Sue McDiarmid, M.D., William Berquist, M.D., Rick Harrison, M.D., and Marvin Ament, M.D.*
*Los Angeles, California*

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Local recurrence of a parathyroid tumor comprises a significant proportion (15 of 145) of possible causes of recurrent or persistent primary hyperparathyroidism. Findings consistent with parathyroid cancer include shorter disease-free interval, higher serum levels of calcium and parathyroid hormone, and histologic appearance. Aggressive surgery can control serum levels of calcium in these patients with acceptable morbidity.

*Douglas L. Fraker, M.D., William D. Travis, M.D., John J. Merendino, Jr., M.D., Mark B. Zimering, M.D., PH.D., Elizabeth A. Streeten M.D., Lee S. Weinstein, M.D., Stephen J. Marx, M.D., Allen M. Spiegel, M.D., Gerald D. Aurbach, M.D., John L. Doppman, M.D., and Jeffrey A. Norton, M.D.*
*Bethesda, Maryland*

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*Atsushi Hiraide, M.D., Masami Katayama, M.D., Hisashi Sugimoto, M.D., PH.D.,*
*Toshiharu Yoshioka, M.D., PH.D., and Tsuyoshi Sugimoto, M.D., PH.D.*
*Osaka, Japan*

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*Thomas R. Weber, M.D., Robert H. Connors, M.D., and Tom F. Tracy, Jr., M.D.*
*St. Louis, Missouri*

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*Kari Haukipuro, M.D., Jukka Melkko, CAND.MED., Leila Risteli, M.D., PH.D., Matti I. Kairaluoma, M.D., PH.D., and Juha Risteli, M.D., PH.D.*
*Oulu, Finland*

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*Hiroshi Tanaka, M.D., Hisashi Sugimoto, M.D., Toshiharu Yoshioka, M.D., and Tsuyoshi Sugimoto, M.D.*
*Osaka, Japan*

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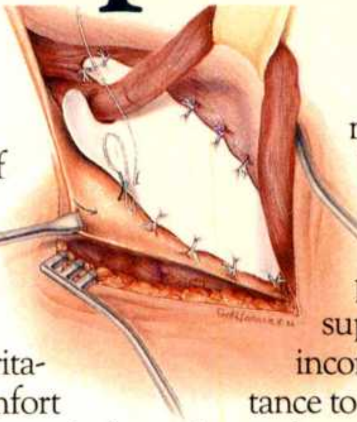

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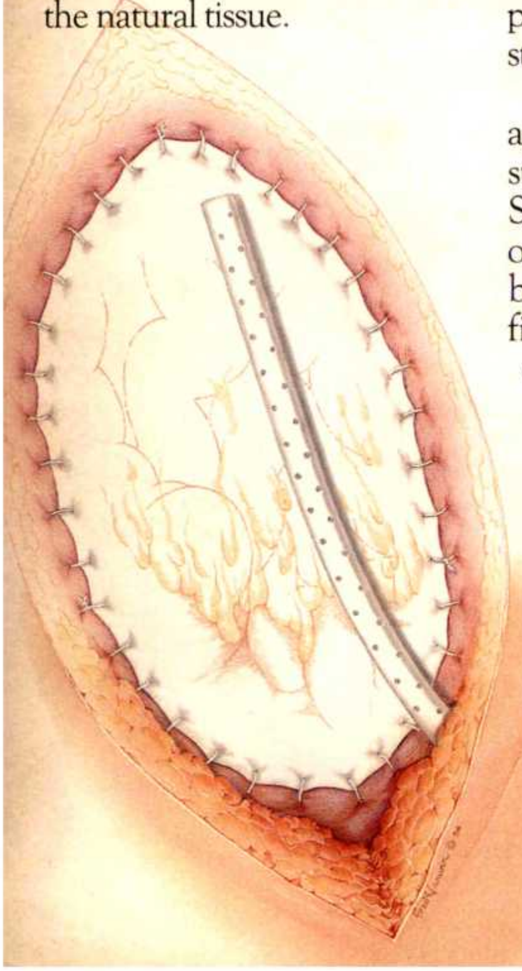

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*Bethesda, Maryland*

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*Charles E. Lucas, M.D.*
*Detroit, Michigan*

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*Gainesville, Florida*

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*Baburao Koneru, M.D., M. Wayne Flye, M.D., PH.D., Ronald W. Busuttil, M.D., PH.D., Byers W. Shaw, M.D., Marc I. Lorber, M.D., Jean C. Emond, M.D., Munci Kalayoglu, M.D., Deborah K. Freese, M.D., and Thomas E. Starzl, M.D., PH.D.*
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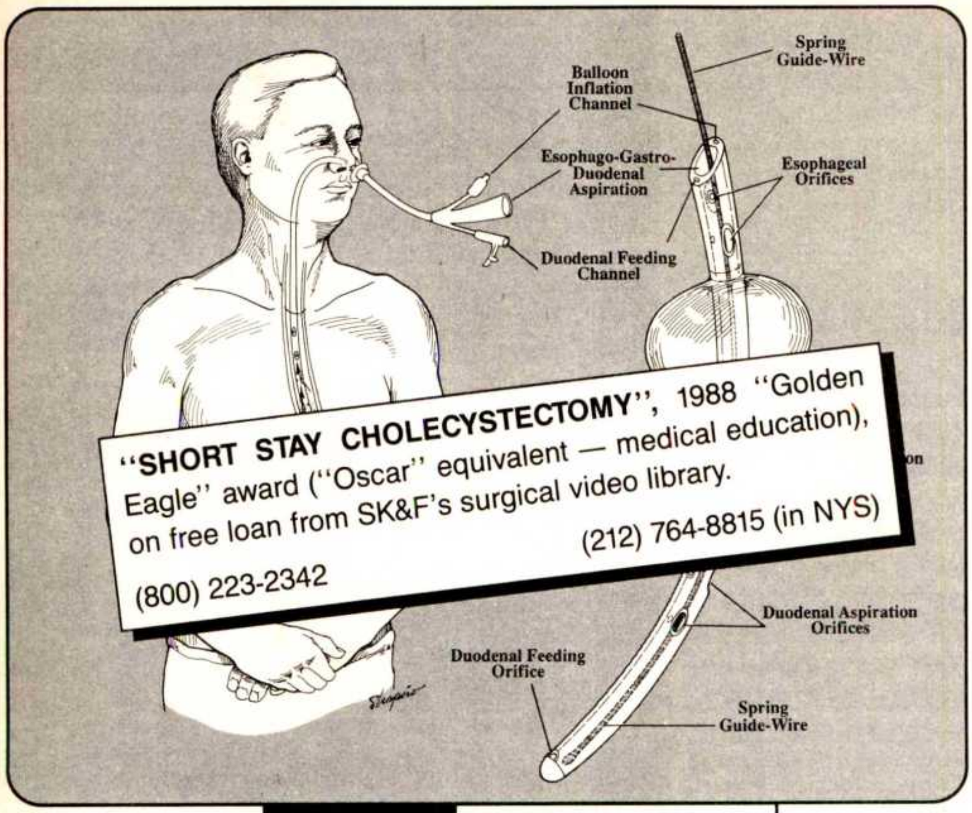

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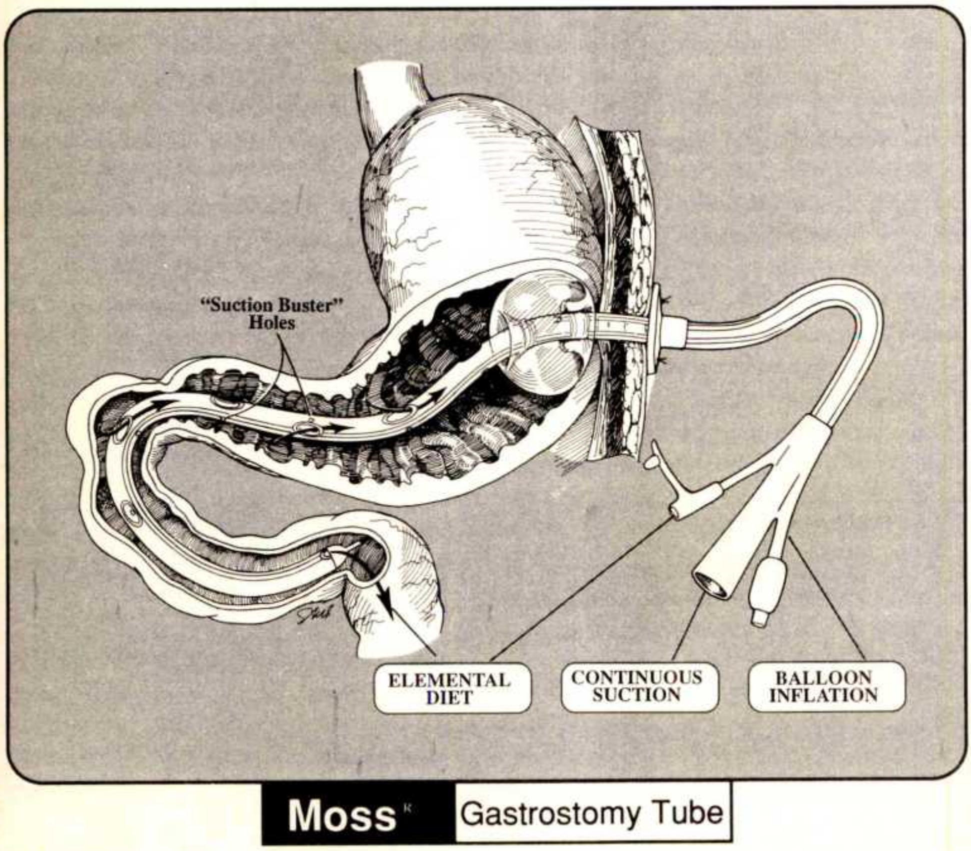

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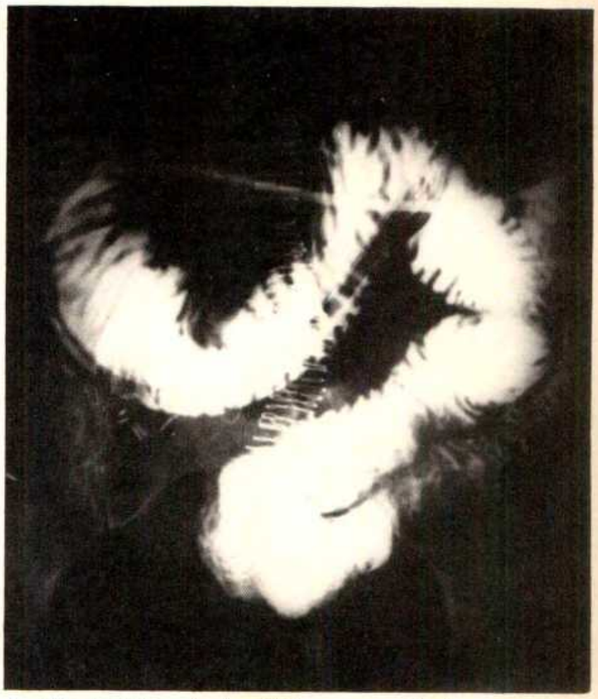
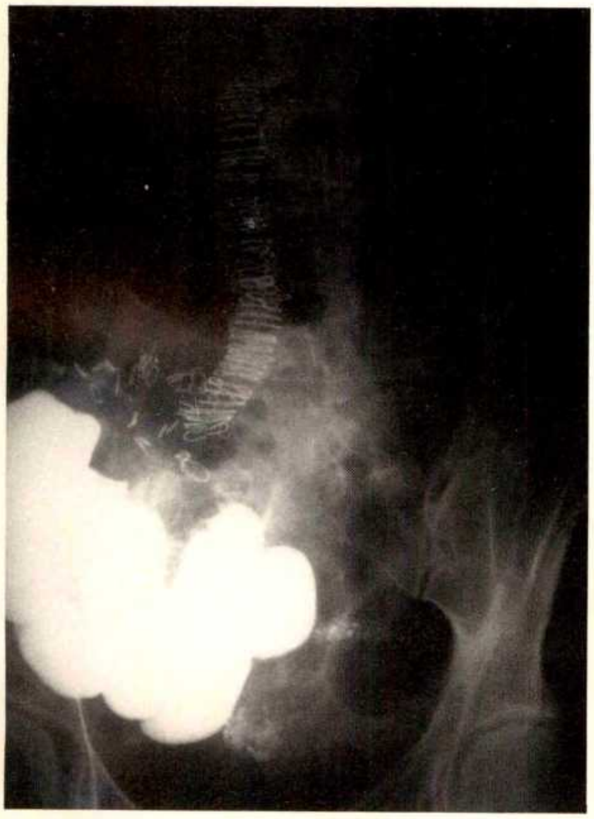
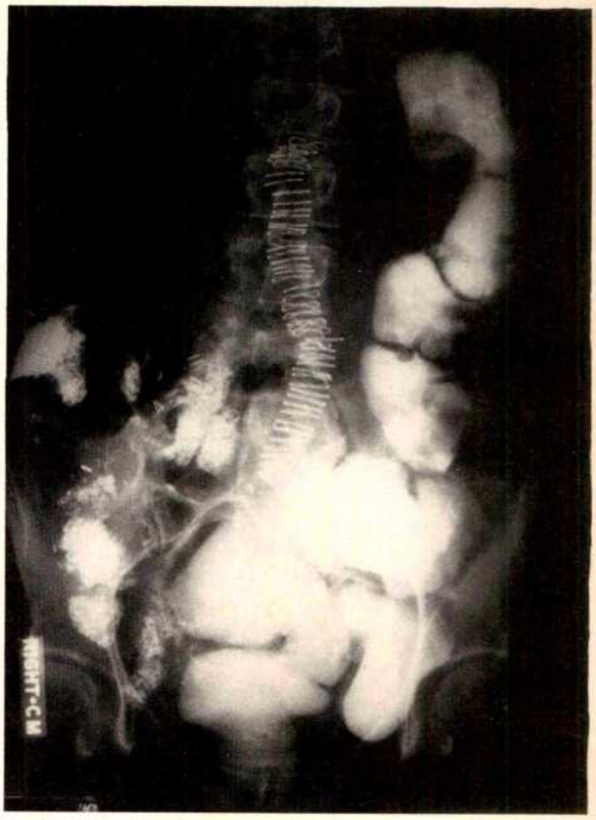


A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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*Burlington and Boston, Massachusetts*

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*J. Ralph Broadwater,* M.D., *Michael J. Edwards,* M.D., *Craig Kuglen,* M.D., *Gabriel N. Hortobagyi,* M.D., *Fred C. Ames,* M.D., *and Charles M. Balch,* M.D.
*Houston, Texas*

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*Dan Poenaru,* M.D., *and Nicolas V. Christou,* M.D., PH.D.
*Montreal, Quebec, Canada*

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*Robert C. Mackersie,* M.D., *Oscar L. Bronsther,* M.D., *and Steven R. Shackford,* M.D.
*San Diego, California*

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*Joel J. Bauer,* M.D., *Marc E. Sher,* B.A., *Herbert Jaffin,* M.D., *Daniel Present,* M.D., *and Irwin Gelerent,* M.D.
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*Charlottesville, Virginia*

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*James J. Pomposelli, M.D., PH.D., Enrique A. Flores, M.D., George L. Blackburn, M.D., PH.D., Steven H. Zeisel, M.D., PH.D., and Bruce R. Bistrian, M.D., PH.D.*
*Boston, Massachusetts*

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*W. Scott McDonald, M.D., Claiborne W. Sharp, Jr., M.B.A., and Edwin A. Deitch, M.D.*
*Shreveport, Louisiana*

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## Erratum

Myers S, Taylor BJ, Stanislawska M. Reperfusion inhibits elevated splanchnic prostanoid production after hemorrhagic shock. Ann Surg 1990; 212:688–693.

Two footnote symbols were published incorrectly in Table 1 (on page 690) of the above-referenced article. The third line of the third column should read 19.0 ± 4.0‡, and the ninth line of the third column should read 11.0 ± 2.8‡.

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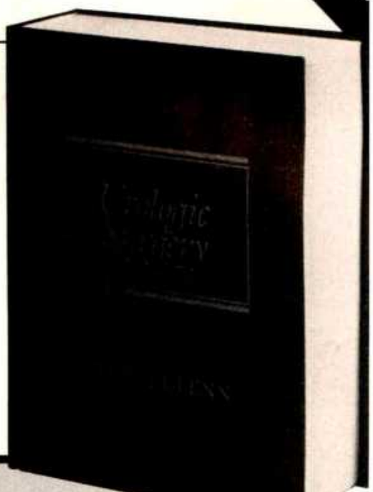

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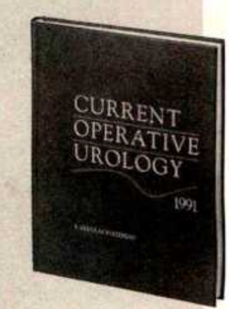

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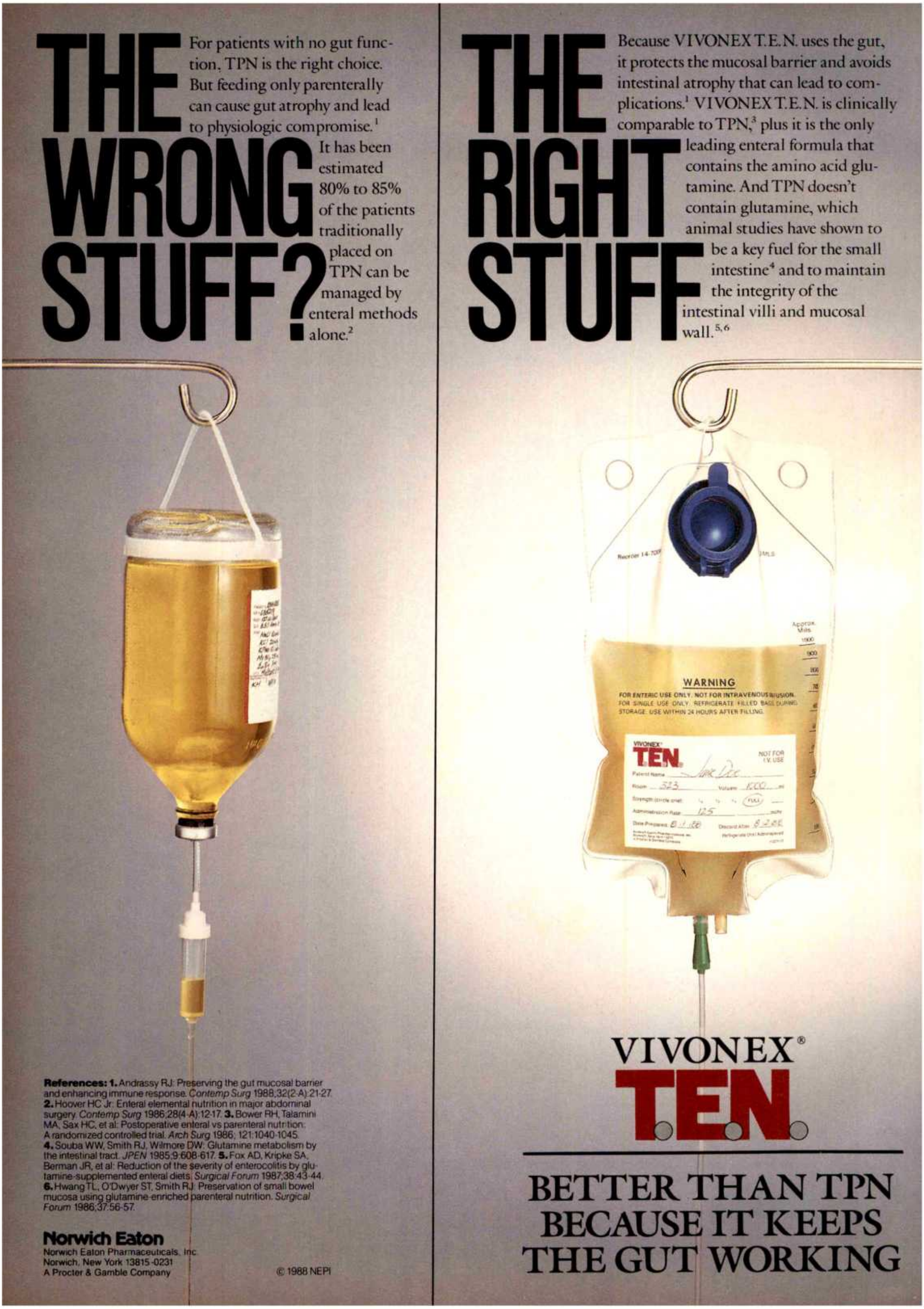

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**References: 1.** Andrassy RJ: Preserving the gut mucosal barrier and enhancing immune response. *Contemp Surg* 1988;32(2-A):21-27. **2.** Hoover HC Jr: Enteral elemental nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. **3.** Bower RH, Talamini MA, Sax HC, et al: Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045. **4.** Souba WW, Smith RJ, Wilmore DW: Glutamine metabolism by the intestinal tract. *JPEN* 1985;9:608-617. **5.** Fox AD, Kripke SA, Berman JR, et al: Reduction of the severity of enterocolitis by glutamine-supplemented enteral diets. *Surgical Forum* 1987;38:43-44. **6.** Hwang TL, O'Dwyer ST, Smith RJ: Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1986;37:56-57.

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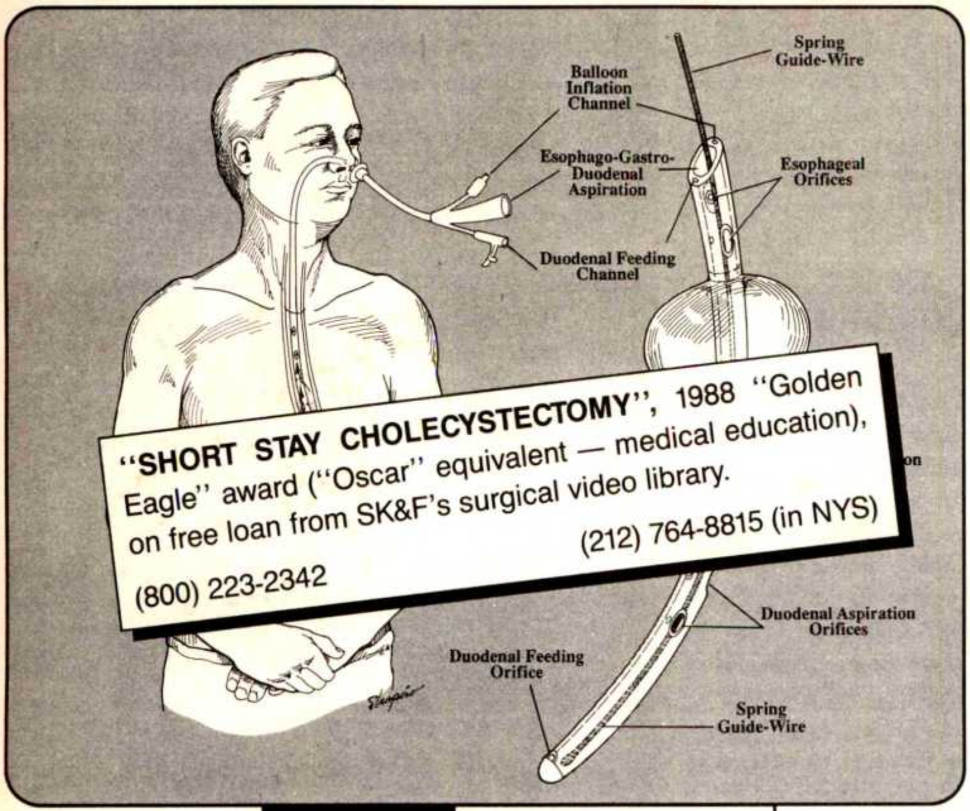

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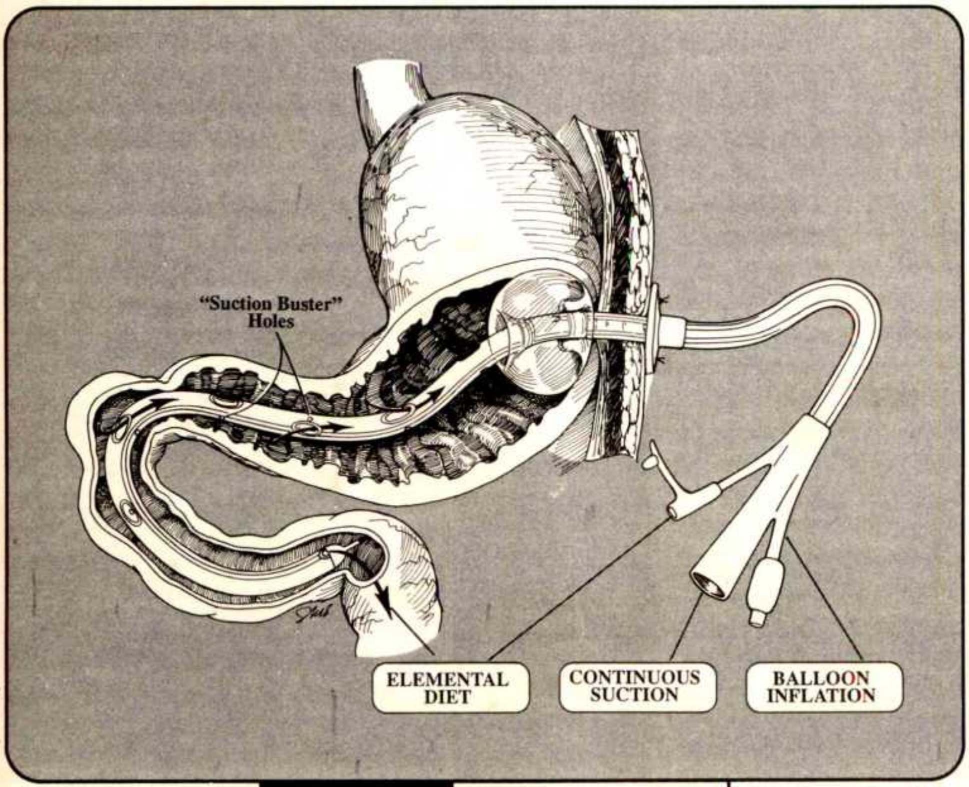

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# EDITORIAL

# Laparoscopic Cholecystectomy

The article by Peters and colleagues, Safety and Efficacy of Laparoscopic Cholecystectomy: A Prospective Analysis of 100 Initial Patients, in this issue of *Annals of Surgery* is one of an increasing number of experiences evaluating this new treatment modality for cholelithiasis. There are approximately 500,000 cholecystectomies performed in this country annually. For decades nearly all these procedures have been performed through a right upper quadrant incision, and this has proved to be an exceedingly safe and effective means of managing cholelithiasis. The hospital mortality rate is less than 1%, morbidity rates are low, and long-term results are excellent, with most patients rendered asymptomatic after cholecystectomy. Despite the outstanding results obtained with standard cholecystectomy, during the past decade a variety of alternative treatment options have been introduced. Many have been pursued enthusiastically, with some encouraging results. None, however, has replaced standard cholecystectomy as the treatment of choice for most symptomatic patients with gallstones.

The newest treatment modality to be introduced for the management of gallstone disease is laparoscopic cholecystectomy. Most surgeons in the United States first became aware of this alternative in 1989 at the Fall Meeting of the American College of Surgeons. Many surgeons greeted this procedure with skepticism, and some with total disdain, because it challenged one of our safest and most effective operative procedures. Nevertheless some surgeons were convinced early on of the procedure's potential and initiated programs in laparoscopic cholecystectomy. Many centers and institutions have now accumulated series comparable in size to the one reported by Peters and colleagues in this issue, with excellent results. The rapidity with which laparoscopic cholecystectomy is gaining acceptance is almost totally consumer driven. Surgeons and hospitals not performing laparoscopic cholecystectomy soon began to lose patients to those who were. Not unlike the changes that have occurred in the management of breast cancer, reluctant surgeons have been prodded by an informed, accepting patient population. Although both standard cholecystectomy and laparoscopic cholecystectomy require general anesthesia, the vast majority of patients undergoing the laparoscopic procedure are discharged the day after surgery, compared to a 2- or 3-day hospitalization following standard cholecystectomy. In addition most patients after laparoscopic cholecystectomy can return to work, participate in sports, and resume all activities by 1 week, and virtually all can by 2 weeks. Vacations do not need to be delayed, time off from work can be nearly eliminated, and the problem of an uncomfortable incision is avoided. In addition most patients think the cosmetic results of the four small incisions required for laparoscopic cholecystectomy are preferable to those of a right subcostal incision.

Despite the rapid and widespread acceptance, early data suggest that some complications are more common after laparoscopic cholecystectomy when compared to standard cholecystectomy. Peters and coworkers report that there was one common duct injury among their 100 patients. Experience from several institutions suggest that the incidence of biliary tract injury, which is 1 in 1000 patients with standard cholecystectomy, is 1 in 100 with laparoscopic cholecystectomy. This incidence may decrease substantially once experience increases. However laparoscopic cholecystectomy, despite the beautiful magnified video display of the right upper quadrant, is done in the absence of three-dimensional depth perception. The fact that the surgeon must perform the operative procedure with a two-dimensional perspective suggests that the incidence of common duct injury may remain higher with this procedure than with standard cholecystectomy. Other complications, such as clips becoming dislodged from the cystic duct resulting in bile ascites, also have occurred with an incidence much higher than after standard cholecystectomy. Cholangiography is more difficult to perform during laparoscopic cholecystectomy and its prevalence will undoubtedly decrease significantly from that during routine cholecystectomy. Whether this will result in a significant increase in the incidence of retained stones remains to be seen. Some institutions are beginning to perform common duct explorations during laparoscopic cholecystectomy by concurrently performing an endoscopic papillotomy and inserting a scope into the common duct from below. Whether this will provide improved results and decreased mortality and morbidity rates compared to standard cholecystectomy and common duct exploration is not known. It probably will be several years before the true morbidity rate for this procedure can be evaluated and compared to standard cholecystectomy.

It is not yet clear what percentage of the 500,000 patients who undergo cholecystectomy each year are candidates for the laparoscopic procedure. In our hospital approximately 80% of all patients undergoing cholecystectomy have the operation performed laparoscopically. This figure may even increase as experience is gained. Cholecystectomy is not the only operative procedure that can be performed laparoscopically. Inguinal herniorrhaphies, appendectomies, and highly selective vagotomies have all been performed through the laparoscope. Other laparoscopic procedures undoubtedly will follow. One prominent department of surgery in Germany has already established a Division of Laparoscopic Surgery.

Currently many hospitals are debating who should be allowed to perform laparoscopic cholecystectomy. Credentialing for this procedure should be well defined, restricted to general surgeons experienced in biliary tract surgery, and should include formal instruction with hands-on animal work, laparoscopic experience, and a period of proctoring by a surgeon experienced with laparoscopic cholecystectomy. National organizations such as the Society for Surgery of the Alimentary Tract, the Society of American Gastrointestinal Endoscopic Surgeons, and the American College of Surgeons have published credentialing guidelines. In addition residency programs should begin to include this procedure in their training programs.

It is healthy and appropriate for surgeons to treat with some skepticism new management innovations, particularly when treating a disease in which there is well-established effective surgical therapy that can be performed with low mortality and morbidity rates. This skepticism, however, should not interfere with the introduction of new procedures that clearly are beneficial. Some aspects of laparoscopic cholecystectomy are contrary to the basic tenants and principles that we learned during our surgical training. Surgery is forever changing, however, and laparoscopic surgery is undoubtedly here to stay. The wonder is not that it was introduced but why it took general surgeons so long, considering that gynecologists have performed abdominal procedures through the laparoscope for decades. Laparoscopic cholecystectomy is proving to be a new and exciting development for general surgery. Careful, cautious experience, such as that reported by Peters and his colleagues in this issue of *Annals*, should be encouraged and will help to clarify the indications, safety, and efficacy of this new surgical procedure.

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# Safety and Efficacy of Laparoscopic Cholecystectomy

## *A Prospective Analysis of 100 Initial Patients*

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**Laparoscopic cholecystectomy quickly emerged as an alternative to open cholecystectomy. However its safety, efficacy, and morbidity have yet to be fully evaluated. During the first 6 months of 1990, we performed 100 consecutive laparoscopic cholecystectomies with no deaths and a morbidity rate of 8% (8 of 100 patients; 4 major, 4 minor). There were 81 women and 19 men, with a mean age of 46.1 years (range, 17 to 84 years). All patients had a preoperative history consistent with symptomatic biliary tract disease, and most had proved gallstones by sonography. This included four patients with acute cholecystitis. Mean operating time improved significantly from month 1 to month 6 (122 ± 45.4 minutes *versus* 78.5 ± 30 minutes, respectively), indicating a rapid learning curve. Mean hospital stay was 27.6 hours, reflecting a policy of overnight stay. Postoperative narcotic requirements were limited to oral or no medications in more than 70% of patients. A regular diet was tolerated by 83% of the patients by the morning following the procedure. Median time of return to full activity was 12.8 ± 6.8 days after operation. In addition analysis of the hospital costs of these 100 cases demonstrates a modest cost advantage over standard open cholecystectomy (n = 58) (mean, $3620.25 ± $1005.00 *versus* $4251.76 ± $988.00). There was one minor bile duct injury requiring laparotomy and t-tube insertion, two postoperative bile collections, and one clinical diagnosis of a retained stone that passed spontaneously. Four patients required conversion to open cholecystectomy because of technical difficulties with the dissection. Although there is a significant learning curve, laparoscopic cholecystectomy is a safe and effective procedure that can be performed with minimal risk. Laparoscopic cholecystectomy should be performed by surgeons who are trained in biliary surgery and knowledgeable in biliary anatomy, and, as with all operations, it should be performed with meticulous attention to technique.**

THE MANAGEMENT OF calculus disease of the biliary tract has undergone significant change during the last decade and clearly is still evolving. Recent years have seen the investigation and development of alternative methods for the management of biliary lithiasis, including gallstone dissolution therapy,[1] endoscopic and percutaneous methods of stone extraction,[2,3] biliary lithotripsy,[4] and the advocation of gallstone removal *via* a 'minilaparotomy.'[5] Yet, despite these technologic 'advances,' most surgeons have continued to manage most patients with gallstone disease with standard operative 'open' procedures. Open cholecystectomy, having now been performed in a similar fashion for more than 100 years,[6] has been an effective method of treating gallstone disease and has been demonstrated to have acceptably low morbidity and minimal mortality rates.[7] Thus open cholecystectomy represents an acceptable risk-benefit ratio for patients and should be regarded as the gold standard against which new therapies are compared. The recent advent of the ability to remove the gallbladder in a fashion identical to open cholecystectomy *via* the laparoscope,[8-10] without formal laparotomy, represents a further advance in the management of biliary disease that seems to have significant merit. This report details an experience with 100 'laparoscopic cholecystectomies' in an effort to study the feasibility and safety of the technique as well as its short-term efficacy in controlling symptoms associated with cholelithiasis.

### Clinical Material

One hundred consecutive patients with symptomatic gallstone disease referred to us between December 1989 and June 1990 were included as the initial study population. All patients were evaluated by one of the authors, the need for cholecystectomy was established, and standard laboratory and radiographic tests were obtained. De-

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Accepted for publication July 18, 1990.

mographic data, including indications for cholecystectomy, weight, height, previous history of jaundice or pancreatitis, and previous surgery, were recorded. All patients underwent preoperative laboratory testing, including complete blood count (CBC), electrolytes, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and abdominal sonogram. The presence of symptomatic gallstones was required for entry into the study. The initial 50 patients were restricted to elective procedures for chronic cholecystitis and cholelithiasis. After this initial experience, the indications were broadened to include acute cholecystitis, as defined by emergency admission with acute right upper quadrant pain, fever, elevated white blood count (WBC), and gallstones on sonography. Known choledocholithiasis was considered a contraindication in this study population.

All patients, with the exception of those presenting with acute cholecystitis, were admitted to the hospital the day of surgery. Oral and intramuscular pain medications were ordered routinely and left to the discretion of the patient. Liquids were provided the night of surgery and a regular diet was resumed the next morning. Most patients were admitted for overnight observation. Follow-up examination was performed as close as possible to postoperative days 7 and 90. Follow-up laboratory studies on these days included CBC, bilirubin, alkaline phosphatase, AST, and ALT. Symptomatic follow-up of the first 50 patients was obtained by telephone more than 3 months after procedure. A standardized questionnaire was used to analyze postoperative pain, nausea, and vomiting, scaled from 1 to 4+ (1 = never had symptom after operation, 2 = occasionally, 3 = frequently, and 4 = daily symptoms). In addition patients were asked if they believed they were cured, improved, or worsened by the procedure and if they would undergo the surgery again under the same circumstances.

### Technique

Nearly all patients were operated on in the supine position, although a few were placed in the lithotomy position, with the operating surgeon standing between the patient's legs, to allow one surgeon to manipulate both sets of instruments. The advantages of the supine position is that it facilitates performance of a cholangiogram and it is easier to proceed to standard cholecystectomy from this position should this become necessary. In addition, as our experience grew, we found that the supine position often allowed a single surgeon to manipulate instruments for both exposure and dissection. Nasogastric tubes and Foley catheters were placed routinely for gastric and urinary bladder decompression, although recently simple straight catheterization of the bladder has been used to avoid an indwelling Foley catheter.

The patients were placed in a 15- to 20-degree head-down position, a small infraumbilical incision was made, and a Verres needle directed toward the midline pelvis was placed into the abdominal cavity for initial $CO_2$ insufflation. Recently we used an open technique (similar to 'open' peritoneal lavage) for insertion of the trochar because it facilitates both initial insufflation and removal of the gallbladder at the conclusion of the procedure. Two to three liters of $CO_2$ were used to insufflate the abdomen while maintaining an intra-abdominal pressure less than 15 mmHg. A standard 10-mm laparoscopic trochar was placed in the subumbilical position. The video laparoscope was introduced into the abdomen through the subumbilical trochar and the pelvic retroperitoneum was inspected for any evidence of hematoma indicating trochar injury. The laparoscope then was directed cephalad and the liver and gallbladder were visualized.

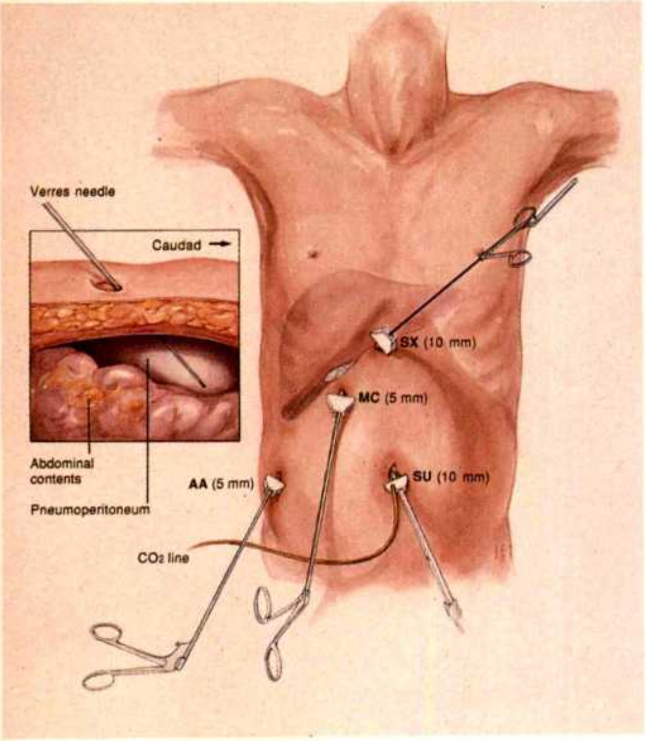
Occasionally intra-abdominal adhesions were encountered, but the laparoscope usually can be maneuvered around the adhesions to the right upper quadrant (RUQ). Additional trocars were placed with video visual control to prevent intra-abdominal injury. An 11-mm trocar was placed in a subxiphoid, midline position, entering the abdominal cavity just to the right of the falciform ligament. This trocar customarily was placed 4 to 5 cm below the xiphoid process, but varied according to the position of the liver. A preliminary inspection of the level of the liver edge and position of the gallbladder allowed for more precise placement. We found it best to keep the skin incisions as small as possible to prevent $CO_2$ leakage around the trocar. A screwing-type motion rather than a direct puncture allowed a more controlled entry into the abdomen. Two 5-mm trocars were placed, one in the right subcostal midclavicular line (MC) and one in the right subcostal anterior axillary line (AA) near the level of the umbilicus (Fig. 1). Grasping forceps were placed in the two lateral trocars and dissecting forceps into the subxiphoid port (SX). Racheted-type self-clamping instruments were preferred in the MC and AA ports so the assistant did not have to squeeze the instrument during the entire case. Initial retraction of the gallbladder was provided by grasping the fundus with the AA forceps (or alternatively the MC grasper), lifting the gallbladder ventrally, and pushing the gallbladder and liver toward the patient's head and right shoulder. This exposed the gallbladder, subhepatic space, and porta hepatis. The neck of the gallbladder above the cystic duct (Hartmann's pouch) was grasped with the MC forceps and pulled toward the AA trocar exposing the porta (Fig. 2).

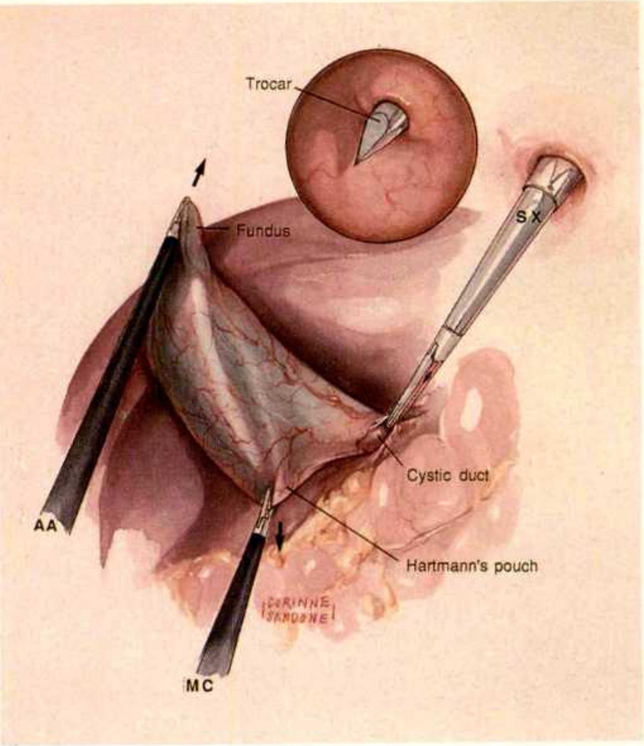
Occasionally adhesions from the gallbladder to the transverse colon were taken down. The surgeon, standing at the patient's left side, inspected the anatomy, identified the cystic and bile ducts, and began the dissection. Because the common hepatic duct typically courses posteriorly and medially, it was difficult to see with a zero-degree angle laparoscope from this perspective. If there is any doubt about the exact nature of the anatomy, the situation can be clarified by inserting a 30-degree laparoscope to allow an alternative viewing angle. For safety, dissection began at the gallbladder neck by bluntly dissecting the fibroareolar tissue overlying the triangle of Calot. Usually this exposed the cystic duct. Dissection continued until the cystic duct was freed circumferetially. Often the cystic artery became evident during this dissection and was freed from its surrounding structures as well. The assistant's hold on the neck of the gallbladder allowed manipulation both anteriorly and posteriorly to the cystic duct by moving the instrument medially and upward to expose the posterior surfaces. Alternatively this maneuvering and countertraction could be done by the operating surgeon once he or she becomes comfortable with the technique. Dissection worked best by taking small bites of tissue with the forceps. Hemostasis was assured by distracting the tissue and applying electrocautery. We routinely tried to identify the junction of the cystic duct with the common hepatic duct, thus clarifying the anatomy. Once the cystic duct and/or artery were dissected circumferetially, the anatomy was inspected again.

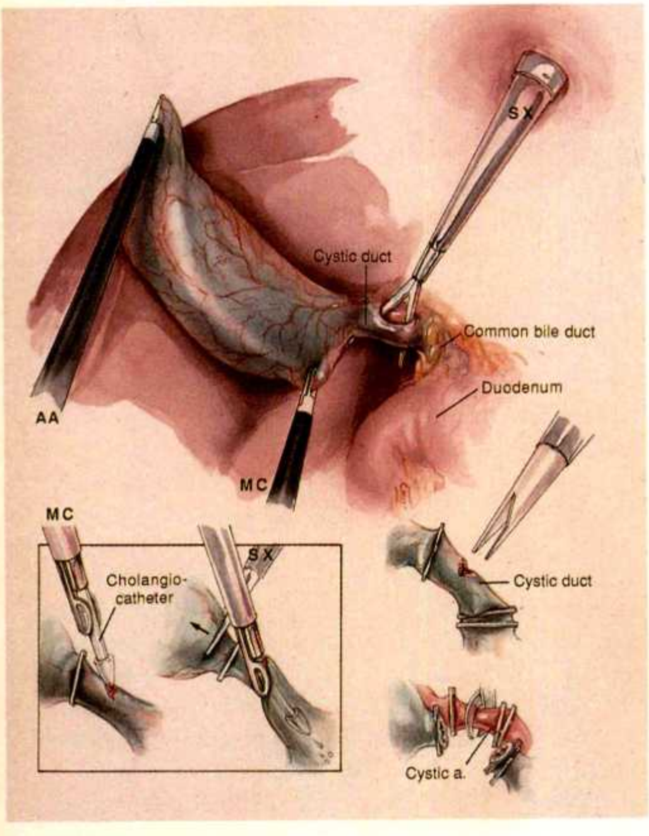
At this stage an intraoperative cystic duct cholangiogram was performed when indicated. A reloadable clipping instrument was placed *via* the SX trochar and a single clip placed onto the cystic duct at the neck of the gallbladder, in preparation for cholangiography. A small nick was made into the cystic duct and a cholangiocatheter placed into it *via* the MC port (Fig. 3). A special instrument (Karl Storz, Culver City, CA) was designed to allow grasping of the cystic duct while feeding the cholangiocatheter through the center of the instrument (a taut catheter was fed retrograde through the instrument before placement). Countertraction was applied *via* the SX port. Saline was infused during placement to ensure patency and prevent air bubbles in the common bile duct. The cholangiocatheter was secured with a clip applied during infusion of saline to assure patency, or with the cholangiocath instrument. Cholangiography was easier when disposable, radiolucent trocars were used. The use of fluoroscopy was preferred because of the amount of hardware present on the anterior abdominal wall (this allows movement of the patient and x-ray machine for an unobstructed view).

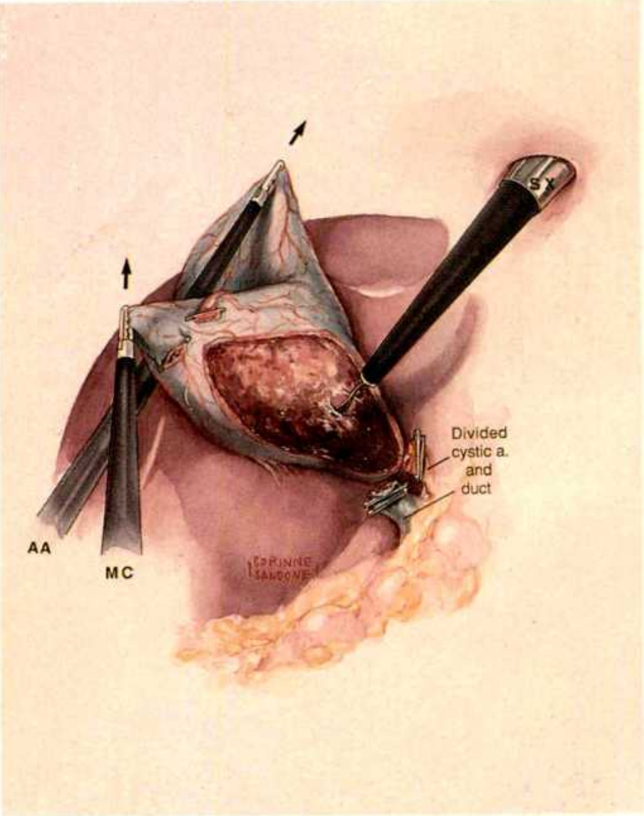
Following satisfactory cholangiography the catheter was removed and two clips were placed on the cystic duct. We were not concerned about leaving long cystic duct remnants and erred on the gallbladder side to avoid common duct injury. The cystic duct was divided with scissors. The cystic artery was dissected free circumferetially, two clips were placed proximally, one distally, and the vessel was divided. At this point it was usually best to reposition the MC grasper on the gallbladder at or just above the transected cystic duct to allow traction upward toward the anterior abdominal wall. This provided tension on the posterior attachments to the gallbladder fossa and allowed dissection of the gallbladder out of its bed (Fig. 4). We abandoned the laser in favor of a spatula-shaped electrocautery instrument because it allows for the combination of cautery with blunt dissection to free the gallbladder. The gallbladder dissection was continued toward the fundus, often requiring the assistance of the grasper through the MC port to maintain optimal tension on the line of dissection. Again the gallbladder can be manipulated *via* the MC instrument medially and laterally to allow for easier dissection. The gallbladder was removed in a retrograde fashion. The neck of the gallbladder was grasped with the MC grasper while the AA grasper held the fundus with forces directed over the top of the liver. As the dissection proceeded, the neck of the gallbladder was pushed over the surface of the liver toward the right hemidiaphragm. When approximately three fourths of the gallbladder was removed, it was helpful to reposition the AA grasper, removing it from its high fundic position and placing it on the reflected posterior portion of the gallbladder just above the line of dissection. This allowed better traction at the line of dissection. Proper traction and countertraction is critical to allow effective cutting of the tissues. Just before removing the gallbladder, while traction can still be maintained on the liver, the portal structures and liver bed were again inspected for hemostasis and proper placement of the clips. The subhepatic space were irrigated free of debris (Fig. 5). The gallbladder then was removed from the liver, maintaining a hold with the AA grasping forceps.

The gallbladder was removed through the SX trochar by grasping the cystic duct with large 10-mm grasping forceps and pulling it into the trochar. Then both the gallbladder and trochar were removed together. Often the volume of stones prevented complete removal through the small puncture site. If so, the gallbladder neck was grasped on the anterior abdominal wall with a Kelly clamp. The fundus was opened outside the abdominal cavity and stones were crushed and removed manually with curved stone forceps (Fig. 6). Occasionally enlargement of the fascial wound was required. This step required considerable patience to avoid spillage. The SX trochar then was replaced and the subhepatic and suprahepatic space were irrigated. A 4- to 5-mm round closed suction drain was placed *via* the MC port when required (Fig. 7). The drain was positioned with an instrument from the SX port, following which the MC trocar was withdrawn over the drain. The $CO_2$ was evacuated and all wounds were closed with a subcuticular suture. Fascial sutures were used only when the fascial incisions at the SX or SU ports were enlarged.



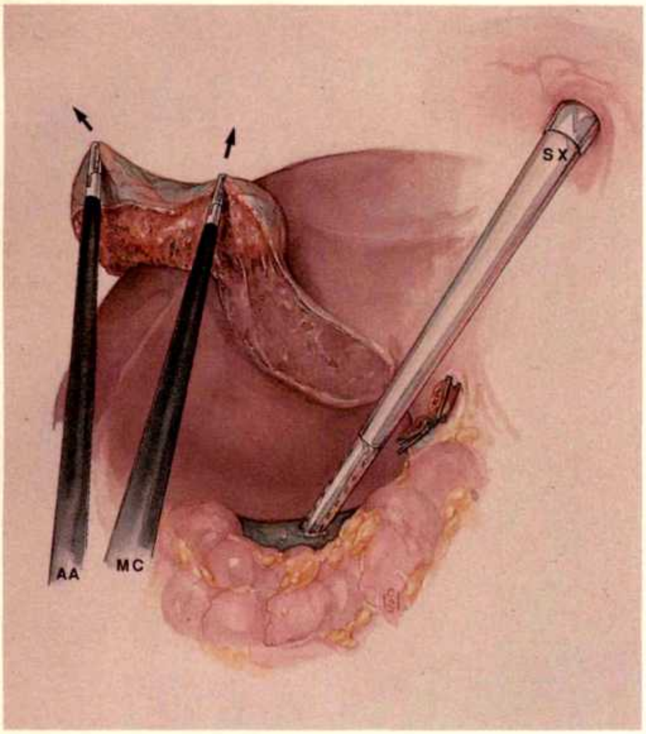


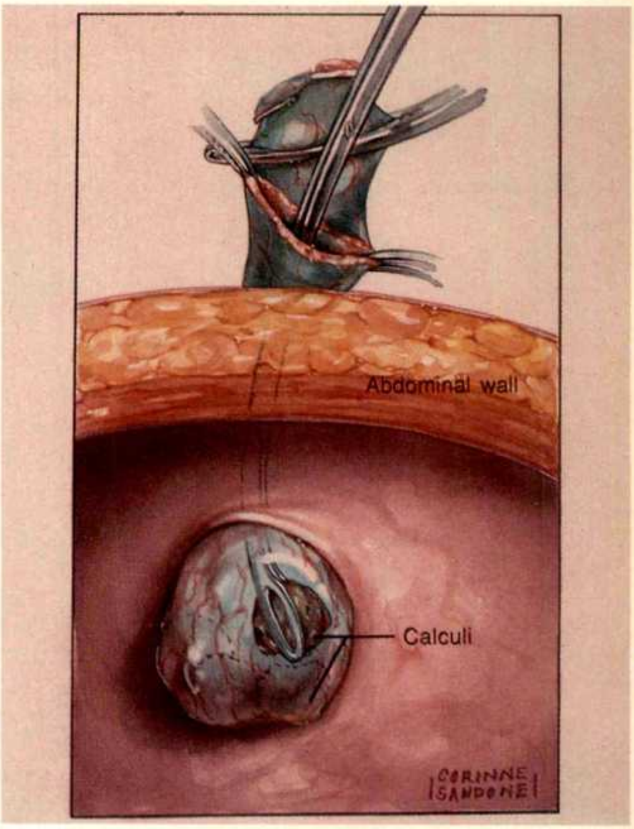




## Results

Demographic data for these 100 patients are demonstrated in Table 1. There were 81 women and 19 men whose average age was 46.1 years (range, 17 to 84 years). All patients had symptomatic biliary tract disease. All but two patients had gallstones demonstrated by preoperative sonography, one patient having had previous lithotripsy





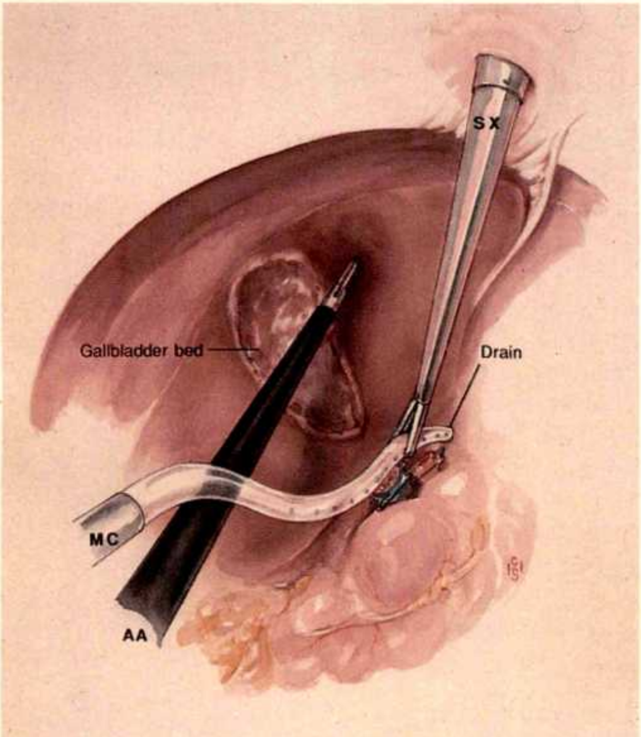


**FIG. 1.** *Facing page, top left.* Trochar placement on anterior abdominal wall. SU, subumbilical, SX, subxiphoid; MC, midclavicular line; AA, anterior axillary line. Inset: Insufflation through verres needle placed subumbilically and directed toward the pelvis. **FIG. 2.** *Facing page, top right.* Initial exposure of the gallbladder and porta hepatis. Note that the SX instrument is the surgeon's port, the AA instrument is commonly used to retract the fundus of the gallbladder toward the head and right shoulder. The MC instrument is used to manipulate the portal exposure *via* a grasp on Hartmann's pouch. **FIG. 3.** *Facing page, bottom left.* Illustration of cystic duct dissection and cystic duct cholangiography, followed by transection of the cystic duct and artery. Cystic duct dissection and cystic duct cholangiography (inset), followed by transection of the cystic duct and artery. Note the clips that have been placed. A single clip is placed distally to prevent flow into the gallbladder during cholangiography, and two clips proximally before transection of the duct. **FIG. 4.** *Facing page, bottom right.* The cystic duct and artery have been transected and the gallbladder is being removed from its bed *via* blunt dissection with a spatula-shaped electrocautery instrument. Tension is maintained on the plane of dissection *via* the MC instrument. **FIG. 5.** *This page, top left.* Just before complete removal of the gallbladder, the liver bed and porta hepatis structures are irrigated clean and inspected for hemostasis. The integrity of the cystic duct and artery clips also are inspected and the anatomy is reviewed. **FIG. 6.** *This page, top right.* The gallbladder is commonly removed *via* the SX port after grasping it with large forceps and pulling the portal end into the trochar. Under direct vision, both outside and inside the abdomen, the stones then often need to be removed manually to allow removal of the gallbladder through the small incision. **FIG. 7.** *This page, bottom left.* Drains are introduced *via* the AA lateral port. The MC port instrument is used to retract the liver while the SX instrument places it in the subhepatic space.

and one having biliary colic in the absence of gallstones. Four patients were admitted 2 to 5 days before surgery with the diagnosis of acute cholecystitis. All four had fever, elevated WBC, and RUQ pain associated with gallstones demonstrated sonographically. One had a previous history of biliary pancreatitis. One had previous history of jaundice.

Laboratory studies for the 100 patients performed before operation, 1 week after operation, and 3 months after operation are shown in Table 2. Thirteen patients had

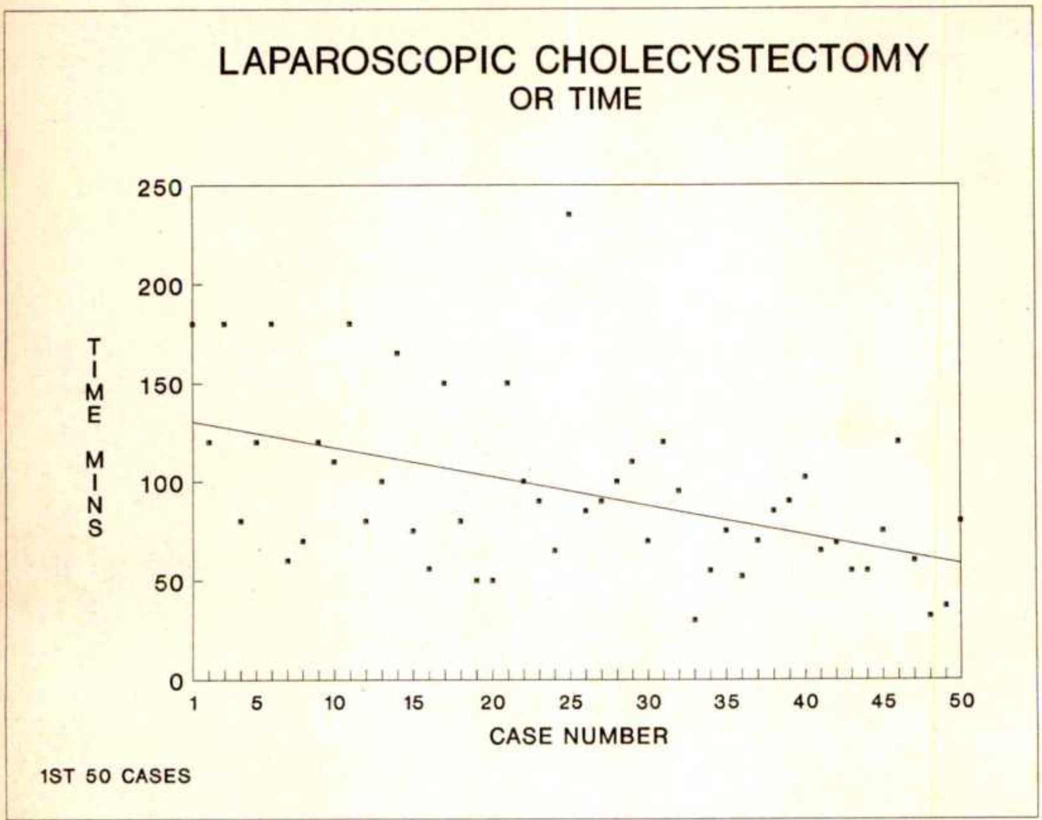


FIG. 8. Trend toward decreased operative time in the first 50 cases.

elevated alkaline phosphatase levels before operation, and four patients had elevated bilirubin levels (1.3, 1.9, 1.1, and 1.1, respectively).

### *Operating Room Data*

All patients underwent general anesthesia with Foley catheters and nasogastric tubes in place. Initial procedures were performed with two attending surgeons and a single consistent camera operator. As our experience grew, the senior resident acted as the operating surgeon, and a scrub nurse as the camera operator. Five attending surgeons participated in the study. Operative time decreased from an average of 122 ± 45 minutes for the first 10 cases to 78.5 ± 30 minutes for the last 10 cases (Fig. 8). Blood loss was minimal in all patients. Early in the series, most dissections were performed with a neodymium:yag laser, which was abandoned in favor of electrocautery after the first 25 to 30 patients.

TABLE 1. *Patient Characteristics*

| Characteristic | Mean | Median | Range |
|---|---|---|---|
| Age (years) | 46.1 | 45 | 17–84 |
| Duration Sxs (days) | 131.7 ± 184 | 78 | 2–1059 |
| Weight (pounds) | 178.6 ± 48.8 | 167 | 85–320 |
| Sex F:M | 81:19 | | |
| Previous surgery* | 45 | | |
| Acute cholecystitis | 4 | | |
| Hx of jaundice | 1 | | |
| Hx of pancreatitis | 0 | | |

± Standard deviation.
* All lower abdominal surgery.
Sxs, Symptoms.
Hx, History

Four patients required laparotomy and cholecystectomy, two for acute inflammation (one of these admitted with acute cholecystitis), making the dissection bloody and difficult. One patient underwent laparotomy because of unclear anatomy. In this patient it was found that the common bile duct had been dissected because it was thought be be the cystic duct. Cystic duct cholangiography (see Technique) was used selectively in eight patients based on a history of jaundice, pancreatitis, or elevated liver function tests. All eight patients had normal cholangiograms. Rarely drains were used at the discretion of the operating surgeon.

### *Complications*

There were no deaths (Table 4). A single intraoperative common bile duct tear occurred in a patient with an inflamed gallbladder. The common duct was dissected through the laparoscope because it was thought to be the cystic duct. Laparotomy revealed a small tear in the anterior common bile duct that was treated by t-tube insertion. Four months after the procedure, this patient's t

TABLE 2. *Laboratory Data*

| Data | Preop (n = 97) | | | POD 7 (n = 80) | | | POD 30 (n = 23) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | Range | Mean | Median | Range | Mean | Median | Range |
| Bilirubin | 0.54 ± .57 | 0.5 | 0.1–1.9 | 0.42 ± .29 | 0.4 | 0–2 | 0.44 ± .2 | 0.4 | 0.2–1 |
| #Abnormal Bilirubin | | 4 | | | 3 | | | 0 | |
| Alkaline Phosphatase | 82 ± 31.5 | 78 | 30–245 | 83.9 ± 40.2 | 83.5 | 0–288 | 81.3 ± 31.4 | 78 | 33–175 |
| # Abnormal Alk Phos | | 13 | | | 12 | | | 3 | |
| ALT | 27.8 ± 20. | 22 | 10–153 | 35.7 ± 56.9 | 24 | 0–457 | 311.5 ± 22.9 | 25 | |
| # Abnormal ALT | | 14 | | | | | | 1 | 12–121 |
| AST | 24.6 ± 8.5 | 23 | 11–61 | 35.2 ± 13.7 | 22 | 0–459 | 28. ± 13.7 | 23.55 | |
| # Abnormal AST | | 14 | | | | | | 0 | 16–82 |

± Standard deviation.

Normals: T Bili; 0.2–1.0, Alk Phos; 37–107, SGPT (ALT); 7–40, SGOT (AST); 12–45.

POD, postoperative day.

tube has been removed and cholangiography and alkaline phosphatase levels are normal. Five patients were readmitted to the hospital from 3 to 10 days after operation. One patient was readmitted with a clinical diagnosis of a retained stone after demonstrating acute biliary colic and elevated bilirubin and alkaline phosphatase levels. By the morning after admission, the patient's pain had resolved, the hyperbilirubinemia abated, and an endoscopic retrograde cholangiogram (ERCP) was normal. It was presumed that she had passed the stone spontaneously. Two patients were readmitted several days after operation with acute RUQ pain and were found to have bile extravasation from the gallbladder bed by biliary scintigraphy (Technetium-HIDA). In both cases ERCP demonstrated bile leakage from small biliary radicles entering the gallbladder fossa. Both were treated with endoscopic placement of 10 french biliary stents across the offending duct. Both resolved within 3 to 5 days. Two patients were readmitted with nonspecific abdominal pain that resolved rapidly.

One patient complained of severe pain localized to his right subcostal area and was thought to have right-sided costochondritis. There were no significant pulmonary complications. There was one urinary tract infection. We observed two instances of infection in the subumbilical wound. Shoulder pain was encountered relatively frequently (in 14 of 100 patients, or 14%), usually in the first week after surgery. Of note gallbladder perforation and bile leakage occurred frequently. An effort was made in each case to remove the spilled stones laparoscopically and irrigate the subhepatic space liberally. Neither early nor late clinical sequelae could be identified in these patients.

*Postoperative Characteristics*

Postoperative characteristics are shown in Table 5. Nasogastric tubes and Foley catheters were removed in the recovery room. Patients routinely were kept overnight, given clear liquids the evening of surgery, a regular diet the next morning, and prescribed intramuscular meperidine or oral oxycodone as needed for pain. Three patients were discharged the evening of surgery; 80 the following day; and 7 patients were discharged on postoperative day 2, including the 4 patients with acute cholecystitis; and 3 patients were discharged on postoperative day 3. Eighty-three per cent of patients were able to tolerate a regular diet by the next morning. Most patients took oral narcotics (71%) until discharge. Twenty-five per cent of patients required no narcotic medication for pain. Patients returned to full activity an average of 12.8 days after surgery (range, 3 to 34 days).

*Cost Analysis*

Mean hospital charges for the 93 patients admitted the day of surgery for elective cholecystectomy was $3620.25

TABLE 3. *Operating Room Data*

| Data | Mean | Median | Range |
|---|---|---|---|
| Time, all cases (min) | 85.27 ± 39 | 75 | 25–235 |
| Time first 10 cases (min) | 122 ± 45.4 | 120 | 60–180 |
| Time last 10 cases (min) | 78.5 ± 30.2 | 65 | 50–145 |
| Laparotomies | 4 | | |
| Laser | 38 | | |
| Electrocautery | 62 | | |
| Introp. cholangiogram | 8 | | |

± Standard deviation.

TABLE 4. *Complications*

| Complication | Number |
|---|---|
| Bile duct injury | 1 |
| Bile leak | 2 |
| Retained stones | 1 |
| Wound infection | 2 |
| Costochondritis | 1 |
| Urinary tract infection | 1 |
| Readmission | 5 |
| Shoulder pain | 14 |

TABLE 5. *Postoperative Characteristics*

| Characteristic | IV | IM | PO | None | |
|---|---|---|---|---|---|
| Narcotic requirement | 2 | 30 | 71 | 25 | |
| (n = 96) | DOS | POD 1 | POD 2 | POD 3 | POD 4 |
| Hospital stay (n = 93) | 3 | 80 | 7 | 3 | |
| Regular diet (n = 95) | 6 | 77 | 9 | 2 | 1 |
| Return to full activity† | 12.8 ± 6.8 days (range 3–34) | | | | |

* IV, intravenous morphine; IM, intramuscular meperidine; PO, oral oxycodone; POD, postoperative day.

† Mean ± standard deviation.

± $1004.00 (Table 6). For comparison mean hospital charges for the previous 58 cholecystectomies (1988 to 1990) that the same group of five surgeons performed in the same hospital was $4251.76 ± $988.00, yielding an average of more than $600.00 savings per case. No attempt was made to evaluate the savings achieved in earlier return to work and increased productivity.

### *Follow-up*

At completion of the trial, an attempt to contact the first 50 patients by telephone was made. For all of these patients, more than 3 months had passed since their procedures. Table 7 demonstrates the results of this survey. Most patients had resolution of their biliary symptoms. All indicated that they were satisfied with the procedure and would undergo it again under similar circumstances. Most patients were eating an unrestricted diet.

## Discussion

Laparoscopic cholecystectomy rapidly emerged as an established method for the treatment of symptomatic gallstone disease. Although a few isolated centers studied the feasibility of the procedure for several years, the fall and winter of 1989 to 1990 brought an explosion of this technique.[10] Reports of its safety, efficacy, complication rate, learning curve, and applicability to the spectrum of biliary tract disease are only now beginning to emerge. Anecdotal reports abound, but little published information exists. The advent of this procedure has raised several issues.

### *The Safety of Laparoscopic Cholecystectomy*

This initial experience with 100 patients demonstrated to us that this is a feasible procedure that the general surgeon and resident can perform safely. The four major complications in the first 100 patients argues for its safety and compares favorably with recent series of open cholecystectomies. Traverso et al.[11] evaluated the 'modern' morbidity of cholecystectomy performed for chronic cholecystitis under elective circumstances. In a series of 671 elective standard cholecystectomies, there were no deaths and a major complication rate of only 4.5%, including three bile duct injuries (0.2%). A morbidity rate of 8% with one bile duct injury (1%) for laparoscopic cholecystectomy compares favorably. There were no complications related to the insertion of the laparoscopic trochar. Whether the morbidity and/or biliary injury rate will change substantially with increasing experience remains to be seen. It also seems clear that laparoscopic cholecystectomy may not be universally applicable to the entire spectrum of gallstone disease. With increasing experience the question becomes not if one **can** perform the procedure under difficult circumstances, but if one **should** perform the procedure given a potentially dangerous situation. It seems that this procedure can be performed as safely as a standard cholecystectomy, as long as patients are selected properly and appropriate caution is exercised.

### *Comparison of Laparoscopic Cholecystectomy Complications with Those of Open Cholecystectomy*

If laparoscopic cholecystectomy is to represent a significant advance in the management of cholelithiasis, morbidity and mortality rates superior to those of standard cholecystectomy should be the goal. Whether this can be achieved awaits a study with larger numbers and a larger variety of patients. Clearly the most significant complication of laparoscopic cholecystectomy is bile duct injury. Anecdotal reports, presentations, and our experience indicate that biliary injury is a real possibility, varying between 0% and 7% in most initial series. Whether this represents an initial learning curve or an inherent hazard of the procedure remains to be proved; however most surgeons would agree that this is a preventable injury. Our single patient who sustained a ductal injury did so under circumstances of chronic cholecystitis, with a contracted short gallbladder and a very short, wide cystic duct that made delineation of the anatomy difficult. The common bile duct was dissected mistakenly for the cystic duct. An

TABLE 6. *Cost Analysis*

| Procedure | Mean | Median | Range |
|---|---|---|---|
| Laparoscopic (n = 93) | $3620.25 ± 1005 | $3436.70 | $1391.80–6091.0 |
| Standard (n = 58)* | $4251.76 ± 988 | $3938.00 | $2591.40–6400.00 |
| Acute laparoscopic (n = 4)† | $6197.25 ± 1156 | $5946.10 | $5199.00–7697.00 |

± Standard deviation.

* Standard cholecystectomies done over 2-year period before to laparoscopic era.

† Acute laparoscopic, acute cholecystitis with laparoscopic cholecystectomy.

TABLE 7. *Follow-up (n = 52)*

| Query | Cured | Improved | Same | Worse |
|---|---|---|---|---|
| Overall Status (n = 52) | 40 (77%) | 12 (23%) | 0 | 0 |
| | Yes | No | | |
| Would have surgery again | 52 (100%) | 0 | | |
| | Never | Occasional | Frequent | Daily |
| Abdominal pain | 43 (83%) | 8 (15%) | 0 | 1 (2%) |
| Nausea* | 37 (80%) | 9 (20%) | 0 | 0 |
| Vomiting* | 36 (92%) | 3 (8%) | 0 | 0 |
| | Unrestricted | Avoid Fat | Severe Restrict | |
| Diet | 36 (71%) | 13 (25%) | 2 (4%) | |

* Some patients did not have these preoperative symptoms.

injury caused by the grasping forceps on the anterior common bile duct was recognized after the abdomen was opened. Such injuries can be prevented by a liberal attitude toward early abandonment of the laparoscopic procedure in favor of an open cholecystectomy. Indeed our threshold for laparotomy has decreased with increasing experience rather than increased, as we learn which patients will prove difficult despite all efforts.

Two instances of symptomatic bile leakage and subhepatic bile collections occurred. Both patients in the early postoperative period developed acute RUQ pain and were shown easily by radionuclide biliary scanning and ERCP to have leaked bile from small accessory ducts entering the gallbladder bed. One patient required percutaneous drainage of the bile collection accompanied by insertion of a 10 french endoscopic biliary stent and quickly resolved her bile collection and symptoms. The stent was removed after 6 weeks with complete healing. The second patient had a very small collection and rapidly improved after stent insertion. She did not require drainage. Whether these stents were necessary and how long to leave them remains unknown. A retrospective review of the operative videotapes revealed no obvious cause of the leaking accessory ducts. In addition we noted that neither a laser technique nor electrocautery seemed to be responsible because the patients were divided between the two techniques. Luschka[12] first demonstrated these small biliary radicles entering directly into the gallbladder bed nearly 100 years ago. Cadaver dissections demonstrated these ducts to be present in 25% to 30% of patients and that significant injury can be avoided by dissection close to the gallbladder wall.[13] We speculate that injury of these small ducts results from the combination of a tearing type of dissection in and around the porta hepatis, along with a dissection where it may be more difficult to maintain directly on the gallbladder wall. What the true incidence is of this complication and whether it can be prevented remains a topic of further study.

A single patient returned with recurrent biliary colic, elevated alkaline phosphatase level, and a bilirubin level of 2.2. A clinical diagnosis of a retained stone was made, she was admitted to the hospital, and ERCP was scheduled the following day. However, by early morning, her symptoms had completely resolved and it was suspected that she passed her stone. Results of the ERCP were normal. Retained common duct stones remain a problem for standard cholecystectomy as well as for laparoscopic cholecystectomy.[14,15] Known choledocholithiasis is considered a contraindication to this procedure. We advocate an attitude of laparotomy and common duct exploration when intraoperative cholangiography demonstrates common duct involvement. The standard of care for common bile duct disease should be no different from how one would manage such disease under the circumstances of open cholecystectomy. However other options exist. The most attractive options are preoperative papillotomy and stone extraction or intraoperative choledocoscopic and laparoscopic common duct exploration. Both procedures have their shortcomings, however. Preoperative identification of common duct stones remains imprecise, leaving a large number of patients with normal (and thus unnecessary) ERCP exams. The techniques of laparoscopic common bile duct exploration are only beginning to emerge, require specialized equipment, significant time to perform, and can be technically difficult. These options should be investigated; however until such time as alternatives to standard care are demonstrated to be efficacious, an attitude toward laparotomy and common duct exploration would seem the most prudent alternative.

Intraoperative and postoperative bleeding represents a theoretical concern. Arterial injury (hepatic or cystic) during the dissection, as well as failure to adequately clip the cystic artery, can result in the need for laparotomy or, of greater concern, the possibility of bleeding after discharge from the hospital. Because of the possibility of cystic arterial bleeding, we usually observed patients in the hospital for 24 hours, although experience may show that this is not necessary.

We observed no significant incidence of major or minor cardiovascular or thrombotic complications. It is unclear whether laparoscopic cholecystectomy differs in this regard or whether it represents a safer alternative in patients with preoperative cardiovascular risk factors. It requires general anesthesia and similar operative times to standard open cholecystectomy, thus one might not expect a significant advantage. Minor complications included two instances of wound infection in the subumbilical wound and a single patient with a urinary tract infection. Right shoulder pain occurred relatively frequently but usually was mild and self limiting. This has been well described in the gynecologic literature and has been attributed to retained $CO_2$.

### *Unresolved Issues*

Many issues remain unresolved with regard to laparoscopic cholecystectomy. There are several major issues. 1) In what clinical setting is this procedure most useful and in which is it difficult and dangerous, *i.e.*, can it, or should it, be applied in the setting of acute cholecystitis, biliary pancreatitis, and choledocholithiasis? Most centers restrict laparoscopic cholecystectomy to chronic cholecystitis and cholelithiasis. This would seem appropriate, especially during the initial learning curve of the procedure. As experience is gained, however, many centers are expanding the indications to include attempts at laparoscopic cholecystectomy in acute cholecystitis, and biliary pancreatitis. Further study is necessary to delineate the spectrum of disease for which laparoscopic cholecystectomy would be the option of choice. 2) Can this procedure be performed safely by the average general surgeon in a community and/or rural hospital? 3) What are the advantages and disadvantages of selective *versus* routine cholangiography in this setting? It seems apparent that the consequences of a false-positive cholangiogram (unnecessary laparotomy or ERCP) tip the balance even further toward a policy of selective cholangiography. 4) What is the optimal method of management of common duct disease when considering or performing this procedure? Opinions vary regarding the proper management of common duct stones with this procedure. As discussed above, options include preoperative ERCP and stone extraction in patients suspected to be at high risk for choledocholithiasis, postoperative performance of the same in those with positive intraoperative cholangiograms, laparotomy and common duct exploration, and laparoscopic common duct exploration *via* choledocoscopy. Definitive answers require further study. 5) Will laparoscopic cholecystectomy afford a means of decreasing morbidity and mortality in high-risk groups of patients requiring elective cholecystectomy? Again proper study of this population of patients is required.

It is clear that laparoscopic cholecystectomy is a useful procedure that has significant, although perhaps not dramatic, advantages over open cholecystectomy. It can be performed safely by experienced surgeons in properly selected patients and it represents a significant and permanent advance in the management of biliary tract disease.

## Acknowledgment

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## References

1. Pitt HA, McFadden DW, Gadacz TR. Agents for gallstone dissolution. Am J Surg 1987; 153;233–246.
2. Martin, DF, Tweedle, DEF. Endoscopic management of common duct stones without cholecystectomy. Br J Surg 1987; 74;209–211.
3. Thistle JL, May GR, Bender CE, et al. Dissolution of cholesterol gallbladder stones by methyl tert-butyl ether administered by percutaneous transhepatic catheter. N Engl J Med 1989; 320: 633–639.
4. Sackmann M, Delius M, Sauerbruch T, et al. Shock wave lithotripsy of gallbladder stones: the first 175 patients. N Eng J Med 1988; 318:393–397.
5. Burhenne, HJ, Stoller, JL. Minicholecystostomy and radiologic stone extraction in high risk cholelithiasis patients: preliminary experience. Am J Surg 1985; 149:632–635.
6. Beal JM. Historical perspective of gallstone disease. Surg Gynecol Obstet 1984; 158:181–189.
7. McSherry CK, Glen F. The incidence and causes of death following surgery for nonmalignant biliary tract disease. Ann Surg 1980; 191:271–275.
8. Dubois, F, Icard P, Berthelot G, et al. Coelioscopic cholecystectomy: preliminary report of 36 cases. Ann Surg 1990; 211:60–62.
9. Reddick, EJ, Olsen DO. Laparoscopic laser cholecystectomy: a comparison with mini-lap cholecystectomy. Surg Endoscopy 1989; 3:131–133.
10. Cuschieri A, Berci G, McSherry CK. Laparoscopic cholecystectomy (editorial). Am J Surg. 1990; 159:273.
11. Gilliand, TM, Traverso, W. Modern standards for comparison of cholecystectomy with alternative treatments for symptomatic cholelithiasis with emphisis on long term relief of symptoms. Surg Gynecol Obstet 1990; 170:39–44.
12. Luschka H. Die anatomie des menschlichen bauches. Tubingen:H. Lauppschen, Bushhandlung, 1863; 255.
13. McQuillan T, Monolas SG, Hayman JA, et al. Surgical significance of the bile duct of Luschka. Br J Surg 1989; 76:696–698.
14. Sawyers JL, Williams LF, eds. Difficult Problems in General Surgery. Chicago: Year Book Medical Publishers, 1989, pp 155–175.
15. Rogers AL, Farha GJ, Beamer RL et al. Incidence and associated mortality of retained common bile duct stones. Am J Surg 1985; 150:690.

**ORIGINAL ARTICLES**

# Computerized Identification of Pathologic Duodenogastric Reflux Using 24-hour Gastric pH Monitoring

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**Duodenogastric reflux is a naturally occurring sporadic event, the incidence, occurrence, and detrimental effects of which have been difficult to assess. The reliability of 24-hour gastric pH monitoring to detect duodenogastric reflux was studied. Central to the use of pH monitoring for this purpose is confidence in its ability to measure and display pH data in a way that reflects changes in the gastric pH environment with sufficient sensitivity. To test this the gastric pH of 10 dogs was measured in the fasting state, after feeding, and after pentagastrin stimulation. The antrum was more alkaline in the fasting state ($p < 0.01$) and the display of data by frequency distribution graph was sensitive enough to reflect induced pH changes. To test the consistency of gastric pH at a given position, simultaneous 24-hour gastric monitoring was performed in 12 normal subjects with two probes placed at either 5 or 10 cm below the lower esophageal sphincter. Only at the 5-cm position did the two probes read within 1 pH unit of each other more than 90% of the time. Based on these principles, gastric pH monitoring was performed 5 cm below the lower esophageal sphincter in 30 normal subjects and 11 patients, fulfilling Ritchie's clinical criteria for pathologic duodenogastric reflux. The data obtained was arranged into 71 variables and subjected to discriminant analysis. Sixteen variables were identified, each with a corresponding coefficient to be used as a multiplier to derive a score. A score of more than +2.2 indicated a high probability of pathologic duodenogastric reflux. The test was applied to a validation population consisting of 10 additional normal subjects and 10 patients meeting Ritchie's criteria. All normal subjects had a normal score and all but one (90%) of the patients had an abnormal score. When compared to O-diisopropyl iminodiacetic acid (DISIDA) scintigraphy in another group of 22 normal subjects and 60 patients, 24-hour gastric pH monitoring was superior in the detection of pathologic duodenogastric reflux. The study shows how the application of computer technology can be used to diagnose pathologic duodenogastric reflux in patients with complex foregut complaints.**

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THE PURPOSE OF the gut is to absorb nutrients and eliminate waste. This is accomplished by moving ingested food through sequential compartments, each with a different pH environment and enzymatic content, where digestion and/or absorption occur. The major determinants of pH in the gastric compartment are acid and mucous secretion, ingested food, swallowed saliva, regurgitated duodenal, pancreatic, and biliary secretions, and the effectiveness of the mixing and evacuation of the chyme. Several methods are available to measure each of these determinants, but the measurements are made only over a short period of time.[1-3] Consequently their effect on luminal gastric pH over 24 hours is unknown. For example the reflux of duodenal juice is measured by analyzing aspirated gastric juice for bile or by O-diisopropyl iminodiacetic acid (DISIDA) scintigraphy, but these tests restrict data sampling to short periods and do not allow for continuous measurement over 24 hours.[4,5]

The monitoring of gastric pH over 24 hours reflects the pH that results from the interaction of gastric pH determinants. Alterations in gastric pH are seen in gastric disorders such as chronic gastritis, gastroduodenal ulcer disease, and gastric neoplasm.[6-8] It was hypothesized that when properly analyzed, 24-hour gastric pH monitoring could provide a means of identifying the determinant responsible for the change in gastric pH and link the observed gastric disorder to an abnormality in a specific pH determinant.

To detect abnormalities in the various pH determinants that make up a 24-hour pH record requires sophisticated analysis. The most common current analysis is a frequency distribution of the pH measurements.[9,10] This is helpful when gross alterations in pH occur, such as reduction in gastric acid secretion by $H_2$ blockers, but lacks sensitivity in detecting more subtle changes such as those produced by duodenogastric reflux and changes in gastric motility.[11-13] A more detailed analysis to expose these

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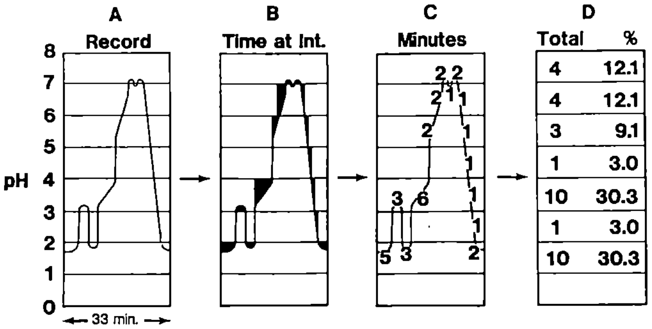
subtle changes has been used by us to detect excessive duodenogastric reflux.

## Purpose and Methods

### *Study 1*

Central to the use of 24-hour gastric pH monitoring is the confidence that displaying pH data by the conversion of the continuous pH record to cumulative exposure at whole-number pH intervals reflects shifts in luminal pH with a high degree of fidelity. To test this 10 mongrel dogs (weighing 15 to 22 kg) were sedated with ketamine and placed in the right lateral position. Two antimony pH electrodes were calibrated with standard buffer solutions of pH 1 and 7. The electrodes were attached to a nasogastric tube so that the tips were 5 cm apart. The distal portion of the nasogastric tube was advanced endoscopically into the duodenum to anchor the gastric pH electrodes 5 and 10 cm proximal to the pylorus. The endoscope was withdrawn into the fundus to allow visual observation of the stomach throughout the test period. Recordings of gastric pH were obtained for 3 hours under four different conditions: (1) fasting, (2) during stimulation of gastric acid secretion by continuous infusion of 2 μg/kg of pentagastrin, (3) after instillation of 100 mL of milk, and (4) during the combination of pentagastrin infusion and instillation of milk.

The gastric pH was monitored continuously on a strip chart recorder and transformed into a format showing the time in minutes that the gastric pH was at a given pH interval (Fig. 1). From this format a pH frequency distribution was derived expressed as the percentage of time the gastric pH was at the pH intervals of 0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, and more than 7 during the monitored period. Median values for each probe were calculated from the 10 dogs. The Wilcoxon matched pairs signed rank test was used to determine statistical significance.



FIGS. 1. A–D. A schematic illustration of the method of conversion of the continuous gastric pH record to cumulative exposure at whole-number pH intervals. (A) A 33-minute segment of a pH record. (B) Blackened areas showing time spent at each pH interval (0–1, 1–2, 2–3, and so on). (C) Conversion of blackened areas to numeric values in minutes. (D) Summation of minutes for each pH interval and their expression as the percentage of the monitored time (33 minutes).

### *Study 2*

The purpose of this study was to determine the probe position within the stomach that would provide the most consistent pH data. Two glass electrodes were positioned 5 cm below the manometrically defined lower esophageal sphincter in 12 normal human volunteers. Twenty-four–hour gastric pH recordings were obtained simultaneously from both electrodes. A diet was given during the recording period that consisted of food with a pH between 5 and 7. The subjects were allowed to move about and pursue normal activity, exclusive of hard work. Body position and time of meals during the monitored period were recorded in a special diary. The same subjects returned for a repeat study with two probes positioned 10 cm below the lower esophageal sphincter.

### *Study 3*

Based on the principles that emerged from the above studies, gastric pH monitoring was performed in normal subjects and patients with clinical evidence of pathologic duodenogastric reflux. The purpose of this study was to identify a pH pattern characteristic of pathologic duodenogastric reflux.

Twenty-four–hour gastric pH monitoring was performed in 30 healthy normal subjects who were free of gastrointestinal complaints, had a normal roentgenographic upper gastrointestinal barium examination, normal esophageal motility, and a normal esophageal acid exposure on 24-hour esophageal pH monitoring. Their gastric pH monitoring records were compared to the records obtained from a test population consisting of 11 patients fulfilling Ritchie's clinical criteria for the diagnosis of pathologic duodenogastric reflux: severe epigastric pain, nausea, bilious vomiting, and acute inflammatory gastritis on endoscopy.[14] These patients also had esophageal motility studies to localize the sphincter for positioning of the probe and gastric analysis to exclude patients with hypersecretion: basal acid output (BAO) > 5 meq/hr and maximal acid output (MAO) > 30 meq/hr.

The symptoms in all of the patients were unresponsive to a variety of medical therapy for a minimum of 6 months. Nine patients had no previous gastric surgery and were repeatedly diagnosed as having 'non ulcer dyspepsia.' Two patients had a previous vagotomy and pyloroplasty. Three patients had a previous cholecystectomy. Although it would appear inappropriate to incorporate patients with a vagotomy and pyloroplasty in the test population, two were included because they represent the most common etiology of the disease.

Twenty-four–hour gastric pH monitoring was performed by placing a pH probe in the stomach 5 cm below the lower border of the distal esophageal sphincter identified by manometry.[15] A diet was given during the test period consisting of food with a pH between 5 and 7. The individuals were allowed to move about and pursue normal activity, exclusive of hard work. Body position, time of meals, and any symptoms experienced during the monitored period were recorded in a special diary.

The 24-hour gastric pH record was divided into four periods: the upright period, the supine period, the prandial pH plateau period, and the postprandial pH decline period (Fig. 2). The prandial pH plateau period was the time the pH remained elevated after ingestion of a meal until the onset of the decline phase. The postprandial pH decline period began when the pH left the prandial plateau level and lasted until it reached the preprandial baseline. The pH baseline was defined as the most common pH less than the pH of 2.

The 24-hour gastric pH data was processed for each of the four different periods. This process transformed the stored pH data into a format that shows the time in minutes that the pH was at a given interval in a manner similar to the animal studies (Fig. 1). From this format the following components were derived (Fig. 3): (1) the pH-frequency distribution expressed as the percentage of time the pH was at the pH interval of 0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, and more than 7 during the monitored period; (2) the duration of pH exposure expressed as the longest time the pH remained at an interval during the monitored period; (3) the frequency of pH change expressed as the incidence of pH movement from a lower into a higher interval during the monitored period; and (4) duration and frequency of pH exposure expressed as the incidence that the pH remained longer than 5 minutes at a pH interval during the monitored period. Formatting the data in this manner, a single 24-hour gastric pH record provided 71 variables for comparing normal subjects and patients with duodenogastric reflux. These variables were subjected to discriminant analysis using a computer program (SPSS Advanced Statistics, Chicago, IL) to select those that were best able to separate patients from normal subjects.

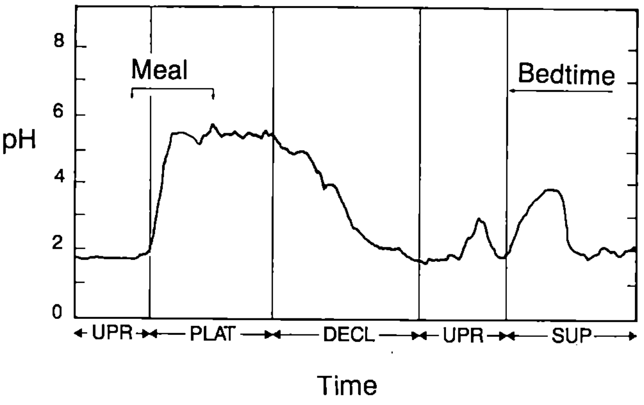
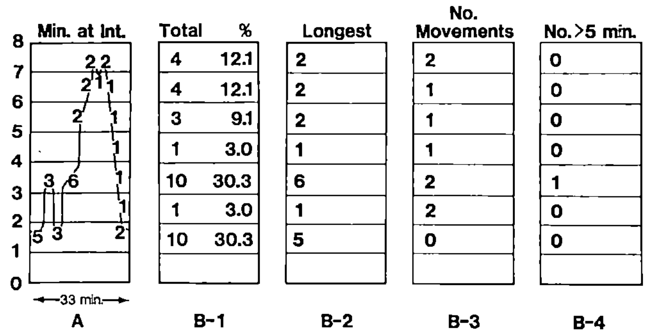


FIG. 2. Division of the 24-hour gastric pH record in different periods: UPR, upright period; SUP, supine period; PLAT, prandial pH plateau period; DECL, postprandial pH decline period.



FIGS. 3A and B. Conversion of the gastric pH monitoring record in humans to the components used for analysis. (A) Numeric value of the time in minutes the pH spent at a pH interval. This was derived according to the method outlined in Figure 1. (B-1) Summation of the time spent at each pH interval and its expression as the percentage of time of the total monitored period. (B-2) Duration of pH exposure expressed as the longest time the pH remained at an interval during the monitored period. (B-3) Frequency of pH change expressed as the incidence of pH movement from a lower into a higher pH interval during the monitored period (calculated from A). (B-4) Duration-frequency of pH exposure expressed as the incidence that the pH remained longer than 5 minutes at a pH interval during the monitored period (calculated from A).

### *Study 4*

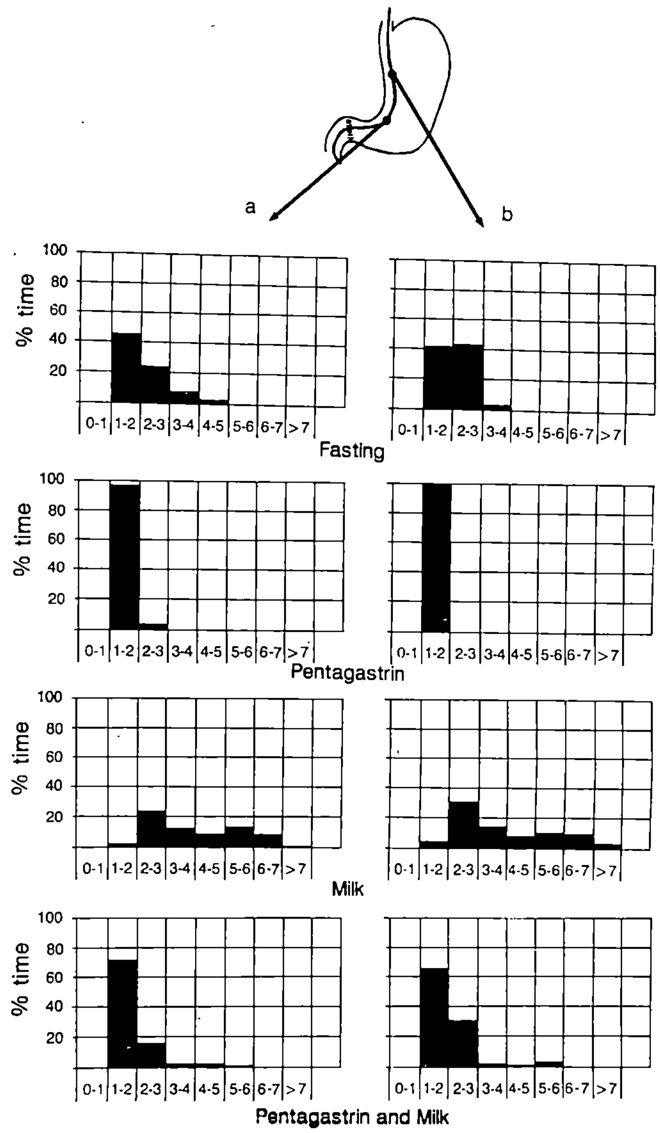
The purpose of this study was to validate the discriminant score's ability to discriminate between normal subjects and those with pathologic duodenogastric reflux. This was assessed using a validation population consisting of 10 normal subjects and 10 patients with duodenogastric reflux according to Ritchie's criteria. These individuals were other than those investigated in Study 3.

Ten normal subjects and ten patients with clinical and endoscopic evidence of pathologic duodenogastric reflux, and fulfilling the same selection criteria as in Study 3, had gastric monitoring for 24 hours. One of these patients had a previous pyloroplasty. Based on the findings of the discriminant analysis performed in Study 3, values for 16 selected variables were obtained from their gastric pH records and scored using a specifically designed computer program.

### *Study 5*

The purpose of this study was to compare 24-hour gastric pH monitoring to the currently accepted method of DISIDA scintigraphy for the detection of pathologic duodenogastric reflux. The study consisted of 22 normal subjects and 60 patients with foregut symptoms of epigastric pain, nausea, and/or bilious vomiting who were stratified on the basis of clinical findings into three groups of increasing probability (possible, suggestive, and likely) for the presence of duodenogastric reflux. The 'possible' group consisted of 22 patients with symptoms of duodenogastric reflux, but no endoscopic or histologic gastritis and a serum gastrin level in the normal range (less than 90 pg/mL); the 'suggestive' group consisted of 28 patients with symptoms and gastritis, but a normal serum gastrin level; and the 'likely' group consisted of 10 patients with symptoms, gastritis, and an elevated serum gastrin level (90 to 400 pg/mL). Patients with achlorhydria were excluded to avoid including those whose elevated serum gastrin level was due to the absence of gastric acidity rather than antral alkalinization by the regurgitation of duodenal juice. Each patient had 24-hour gastric pH monitoring, as previously described, and DISIDA scintigraphy in an attempt to document the presence of duodenogastric reflux. Analysis of the 24-hour gastric pH record was done without knowledge of the clinical condition of each subject using a computer program developed in the previous studies and available from Gastrosoft Inc, Irving, Texas.

Diisopropylacetanilido imidodiacetic acid scintigraphy was done after an overnight fast. Individuals were placed in the supine position under a gamma camera fitted with a low-energy, all-purpose collimator. The photopeak of the energy window was set at 140 keV ± 20%. Five millicuries of Tc99m DISIDA was administered intravenously. Abdominal images were obtained immediately after injection and at 5- minute intervals for 60 minutes and stored. If no duodenogastric reflux was observed after 60 minutes, 20 $\mu$g/kg of synthetic C-terminal octapeptide of cholecystokinin (CCK) was injected intravenously during 5 minutes and imaging was continued for 30 minutes more. Reflux of duodenal contents into the stomach was recognized by an increase of radioactivity in the area of the stomach after Tc99m-DISIDA injection with or without stimulation with CCK. The position of the stomach was identified by drinking a Tc99m pertechnate water solution at the end of the study. The scans were interpreted by one of the authors (NCG) without knowledge of the clinical condition of each subject. The Fisher exact test was used to determine statistical significance.



FIGS. 4a and b. The median percentage of time the gastric pH was at a pH interval during the monitored period in the fasting state, while stimulated with pentagastrin, after the instillation of milk, or after pentagastrin stimulation and the instillation of milk. Because median percentages are plotted, their sum does not equal 100%. (a) Antral probe. (b) Corporal probe.

## Results

### *Study 1*

The pH distribution in 10 fasting dogs measured 5 and 10 cm proximal to the pylorus is shown in Figure 4. In the fasting state, the baseline pH was in the interval between 1 and 4 for the majority of the measured time for both probes. The distal pH electrode recorded a pH in the interval of 2–3 for 25.2% of the time compared to 44% for the proximal probe. This difference was significant ($p < 0.01$), indicating a more acidic environment in the proximal stomach.

The stimulation of gastric acid secretion caused an increase in the time spent at the pH interval of 1–2 from 46.7% to 96.3% and 41.3% to 100% in the corpus and antrum, respectively ($p < 0.05$) (Fig. 4).

Instillation of milk into the stomach caused an instantaneous increase in pH measured by both probes, and the pH distribution over the monitored period shifted toward alkalinity (Fig. 4), that is, a significant increase in the percentage of time the pH was at the intervals 5–6 ($p < 0.01$), 6–7 ($p < 0.05$), and more than 7 ($p < 0.05$). The pH returned gradually to its baseline level with evacuation of the milk from the stomach. This occurred within a median of 121 minutes (range, 75 to 180 minutes) in the corpus and 69 minutes (ranges, 19 to 180 minutes) in the antrum.

This was associated with a shift to the pH distribution seen in the fasting state.

Simultaneous administration of pentagastrin and instillation of milk resulted in an instantaneous rise in gastric pH measured by both probes. The pH distribution showed that the percentage of time spent at the pH interval 1–2 was midway between that observed for the fasting state and pentagastrin infusion alone (Fig. 4). As expected there was also a faster return to the initial baseline pH; corpus, 24 minutes (range, 2 to 46 minutes); antrum, 15 minutes (range, 2 to 43 minutes).

These results indicate that the conversion of the continuous gastric pH plot to cumulative exposure at whole-number pH intervals accurately reflects induced changes in intraluminal gastric pH. This was true for the probe in the antrum as well as in the corpus. The finding of a statistical difference between the corporal and the antral probe in the fasting state stresses the importance of knowing the position of the probe in the stomach.

### *Study 2*

Table 1 shows that when two probes were placed 5 cm below the lower esophageal sphincter, the percentage time the two probes were within 1 pH unit of each other was more than 90% in the upright and supine positions during the fasting state. This was not true for the 10-cm position in the supine position. A large variability occurred during the meal and postprandial period.

These results show a remarkable consistency of pH data when the probes are positioned 5 cm below the lower esophageal sphincter during the fasting state, and indicate that this probe position should be used for clinical monitoring. It also indicated that the prandial period should be analyzed separately.

### *Study 3*

Table 2 shows the 16 variables identified by the computer from the 71 variables available as discriminating between normal subjects and patients with duodenogastric reflux and the calculated corresponding coefficient for each variable to be used as a multiplier of the measured value to arrive at a final score for each patient. The higher the score, the greater was the probability that an alkaline pH change was due to duodenogastric reflux. When applied to the studied population, the score results in a complete separation between normal subjects and patients with the abnormality (Fig. 5). The scores in the normal subjects ranged from −5 to +0.8 and in the patients from +3 to +8. On the basis of this analysis, a patient with a

TABLE 1. *Simultaneous 24-hour Gastric pH Monitoring with Two Probes in 12 Normal Subjects*

| Probe Position in Centimeters Below LES | Percentage Time within 1 pH Unit* | |
|---|---|---|
| | Upright | Supine |
| 5 and 5 | 93.5 | 91.3 |
| 10 and 10 | 91.2 | 77.7 |

* Meal and postprandial period excluded.
LES, lower esophageal sphincter.

TABLE 2. *Selected Variables and Corresponding Discriminant Function Coefficients Derived from the Test Population*

| Variable | Coefficient |
|---|---|
| 1. Baseline pH | +5.823333 |
| 2. Plateau pH | −1.399631 |
| 3. Percentage time in supine position at pH >7 | +17.20774 |
| 4. Percentage time in supine position at pH interval 4–5 | −0.8122231 |
| 5. Percentage time in supine position at pH >7 | −1.944237 |
| 6. Percentage time in decline phase at pH interval 2–3 | +0.1672585 |
| 7. Percentage time in decline phase at pH interval 4–5 | +0.7117193E-01 |
| 8. Percentage time in decline phase at pH >7 | +4.957498 |
| 9. Longest time in upright position at pH interval 4–5 | +0.1022607 |
| 10. Longest time in upright position at pH interval 5–6 | −0.1186103 |
| 11. Longest time in upright position at pH >7 | −14.15213 |
| 12. Longest time in supine position at pH interval 3–4 | −0.2490881E-01 |
| 13. Longest time in supine position at pH >7 | +0.4339899 |
| 14. No. of episodes in upright position, pH >7 | +24.39451 |
| 15. No. of episodes > 5 minutes in upright position pH interval 3–4 | +1.657163 |
| 16. No. of episodes > 5 minutes in upright position pH interval 4–5 | +2.722760 |

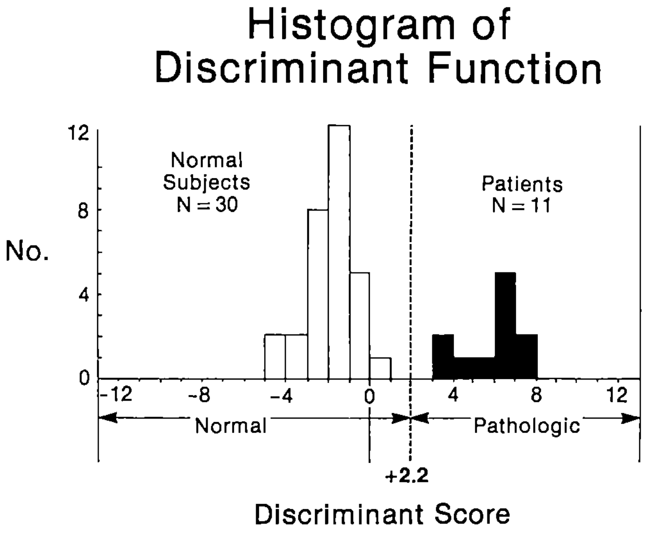


FIG. 5. Histogram of the gastric scores from the test population. A clear discrimination is shown between normal subjects and patients with clinical symptoms and signs of duodenogastric reflux.

score of +2.2 or more had a high probability of having pathologic duodenogastric reflux.

*Study 4*

Figure 6 shows the results of calculating the discriminant scores for the individuals in the validation population. All normal subjects had a normal score and all but one (90%) of the patient population had an abnormal score. This confirmed the validity of the scoring system to detect pathologic duodenogastric reflux.

TABLE 3. *Comparison of TcHIDA and 24-hour Gastric pH Monitoring*

| Test of DER | Normals | Patients with Clinical Evidence of DGR<br>Possible | <br>Suggestive | <br>Likely |
|---|---|---|---|---|
| n | 22 | 22 | 28 | 10 |
| DISIDA positive | 18% | 41% | 64% | 50% |
| 24-hour pH positive | 0% | 18% | 54% | 80%* |

* $p < 0.05$ *versus* normals, and patients with possible and suggestive DGR. DGR, duodenogastric reflux.

*Study 5*

Table 3 shows a comparison of the prevalence of a positive DISIDA scan and 24-hour pH monitoring in patients with progressively greater clinical evidence of pathologic duodenogastric reflux. The DISIDA scan was positive in 18% of normal subjects and the prevalence of a positive scan did not increase with increasing probability of disease on a clinical basis. In contrast the 24-hour gastric pH discriminant score was normal in all control subjects and the prevalence of a positive score increased in parallel with increasing probability of disease on a clinical basis. There were significantly more patients with 'likely' duodenogastric reflux who had a positive 24-hour gastric pH score than normals and patients with 'possible' and 'suggestive' duodenogastric reflux. This was not so for DISIDA.

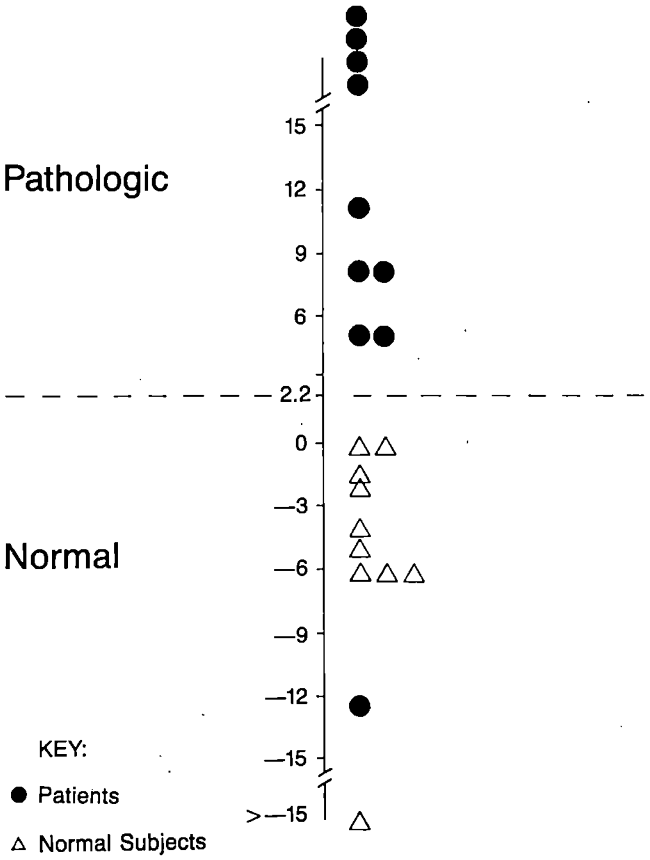


FIG. 6. Results of the discriminant score applied to the validation population.

## Discussion

Clinical medicine has advanced by retrospective analysis relating symptoms to anatomic lesions and using this relationship prospectively to diagnose disease. Symptoms, however, can occur before the development of specific anatomic lesions, resulting in the inability to confirm the presence of disease. To recognize the cause of these symptoms requires detection of the abnormal function. Excessive duodenogastric reflux is such an abnormality.[14,16-19] It is a natural event, but when increased causes the symptoms of epigastric pain, nausea, vomiting, and, if persistent, gastric mucosal damage.[2,20-22] The incidence, occurrence, and detrimental effect of excessive duodenogastric reflux have been difficult to assess with current techniques.[1,2,4,23] Its most commonly accepted pathologic occurrence is in the surgically altered stomach, but even here the event has been difficult to study and define accurately.[24-27] There is a definite need to determine to what extent duodenogastric reflux exists in normals, and when present in excess, what role it has in the pathogenesis of upper gastrointestinal tract disease.

Ritchie[14,24] defined excessive duodenogastric reflux on a symptomatic basis. According to him it can be diagnosed if the symptoms of epigastric pain, intermittent nausea, and bilious vomiting occur in patients with histologic evidence of chronic gastritis. The use of this definition is most apt to detect those patients with a profound abnormality. Because the symptoms are fairly nonspecific and occur frequently in patients with upper gastrointestinal tract complaints, a full constitution of symptoms and histologic gastritis must be present to prevent excessive diagnosis of the abnormality. Patients with atypical or less than three typical symptoms are passed over as having 'nonulcer dyspepsia.' A dependable method is needed to identify the patients in this group who have excessive duodenogastric reflux.

Tests used to diagnose pathologic duodenogastric reflux include sampling of gastric content for bile salts, endoscopy and biopsy, provocative test, and external scanning after intravenous injection of a bile-secreted radionuclide.[1,2,5,14,23,28–31] None of these, singly or in combination, can define patients suffering from excessive duodenogastric reflux with a high degree of dependability because the disorder is due to an increased frequency of sporadic reflux events.[5,32] The problem with these tests is that they are limited to isolated 'dip stick' sampling rather than measurements made over a prolonged period of time. The purpose of this study was to introduce 24-hour gastric pH monitoring as a means to measure excessive duodenogastric reflux. To do so required defining the disease associated with excessive duodenogastric reflux with the best clinical criteria, identifying a patient population on the basis of the criteria, and using discriminant analysis to differentiate the gastric pH record between normal subjects and patients with the disease. The latter would characterize the gastric pH record associated with the entity. A discriminant scoring system was developed and tested in a validation population selected by the same criteria as the original test population. The results confirmed the ability of the score to separate patients with a high probability of having excessive duodenogastric reflux from normal subjects. The test was compared to the currently accepted method of DISIDA scintigraphy to detect pathologic duodenogastric reflux. The finding that the prevalence of a positive 24-hour gastric pH monitoring test paralleled clinical evidence of disease more closely than DISIDA scintigraphy gave us the confidence in the test to identify the presence of excessive duodenogastric reflux in patients with less typical symptoms.

The development of computerized ambulatory pH monitoring systems for the esophagus made outpatient 24-hour pH monitoring of the stomach practical.[33] Gastric pH monitoring has been used to evaluate the effect of drugs on acid secretion, but its diagnostic potential and usefulness in understanding the pathophysiology of gastric disease has been neglected.[10–12,34–36] Little[37] suggested this application while investigating the pathophysiologic causes of alkaline reflux esophagitis. He assumed that alkalinity in the stomach reflects duodenal regurgitation and acidity in the esophagus reflects gastric regurgitation. With experience it became clear that the alkaline change in the stomach was not always indicative of duodenogastric reflux and that the determinants of intraluminal gastric pH were more complex than the determinants of intraluminal esophageal pH. This called for a discriminant analysis of the pH record to identify those patients with excessive duodenogastric reflux. Sixteen of the seventy-one pH parameters evaluated were found to have discriminative power (Table 2). Each of these has a discriminant coefficient used to multiply the measured value, and when summed gives a score regarding a patient's probability of having excessive duodenogastric reflux. Although it would have been preferable to identify 1 of the 16 parameters as an indicator for excessive duodenogastric reflux, this failed. The power of a multivariant discriminant analysis was needed. The individual parameters of the discriminant analysis with a high positive or negative multiplier provided insight into the detection of the abnormality. For example the discriminant coefficient for parameter 11, that is, the maximum duration the pH remained at a pH greater than 7 in the upright position, was −14.15 (Table 2). This appears paradoxical to parameter 3 because its discriminant coefficient is +17.2 for the percentage time in the upright position that the pH was greater than 7 (Table 2). At first sight it seems illogical that a prolonged duration of pH greater than 7 will decrease the score, whereas the percentage of time spent at more than pH 7 will increase the score. Further thought suggested that how the exposure above pH 7 occurs is important in the detection of the disease, that is, frequent exposures of short duration are more suggestive of pathologic duodenogastric reflux than is sustained exposure. This is confirmed by the high positive multiplier of 24.39 for parameter 14, that is, the incidence the pH moved from a lower pH interval into an interval greater than 7 in the upright position (Table 2).

The use of 24-hour gastric pH monitoring and its discriminant analysis to diagnose duodenogastric reflux supports the concept that altered intraluminal pH patterns reflect altered gastrointestinal function. The concept of recognizing disease from a pattern of sequentially recorded pH data is similar to using histologic patterns to recognize disease processes such as neoplasia, inflammation, or ischemia. For example, as the pathologist identifies histologic patterns that have a high probability of being caused by a specific diseased process, the computer identifies patterns in luminal pH that have a high probability of being caused by a specifically altered gastrointestinal function that, if persistent, may cause mucosal damage. A good example of the latter is gastroesophageal reflux disease in which altered pH exposure of the esophagus can identify the presence of the disease before any histologic changes in the mucosa.[38]

The gastrointestinal tract is composed of compartments separated by sphincters. Each compartment has distinct pH characteristics suitable for the action of specific enzymes. The acidic gastric compartment is bounded by the relatively alkaline pH environment of the esophagus proximally and by the duodenum distally. Alterations in the pH environment of a compartment can result in activation of inappropriate enzymes, which leads to mucosal damage and disease.[38,39] Indeed, in the present study, specific pH changes in the gastric environment were linked to symptoms and mucosal damage.

The goal of this study was to develop a computer-generated discriminant score to identify pathologic duodenogastric reflux. This was done by discriminant analysis of 24-hour gastric pH recordings from patients with classical symptoms and findings of the disease. It is anticipated that the use of this computer-generated score will be helpful to diagnose the disease in patients with less typical symptoms and institute therapy before the development of mucosal damage. The computer's unique capacity, in this regard, is its ability to analyze data obtained over a circadian cycle and identify patterns that are predictable of an abnormality. Discriminant analysis of 24-hour gastric pH monitoring, as described in this report, has been used to identify patients with pathologic duodenogastric reflux who have been successfully treated with bile diversion surgery, giving further validity to the test.[40]

## References

1. Begemann F, Schumpelick V. Problems in duodenogastric reflux assessment using bile acids and lysolecithin measurement. Scand J Gastr 1981; 16(Suppl):51–54.
2. Müller-Lissner SA, Fimmel CJ, Sonnenberg A, et al. Novel approach to quantify duodenogastric reflux in healthy volunteers and in patients with type I gastric ulcer. Gut 1983; 24:510–518.
3. Baron JH, Griffen WO, Alexander-Williams J. Use and abuse of gastric functions tests by British and American gastric surgeons. Dig Dis 1975; 20,4:370–376.
4. Schumpelick V, Stemme D, Begemann F. Ulkuskrankheit und duodenogastraler Reflux. Z Gastroenterologie 1983; 21:11–20.
5. Müller-Lissner SA, Fraass C. Dissociation of duodenogastric marker reflux and bile salt reflux. Dig Dis Sci 1985; 30:733–738.
6. Dragstedt LL. Pathogenesis of gastroduodenal ulcer. Arch Surg 1942; 44:438–451.
7. Byers F, Jordan PH. Effect of bile upon gastric mucosa. Proc Soc Exp Biol Med 1962; 110:864–866.
8. DuPlessis DJ. Pathogenesis of gastric ulceration. Lancet 1965; i: 974–978.
9. Emde C, Garner A, Blum AL. Technical aspects of intraluminal pH-metry in man: current status and recommendations. Gut 1987; 28:1177–1188.
10. Walt R. Twenty-four hour intragastric acidity analysis for the future. Gut 1986; 27:1–9.
11. Fimmel CJ, Etienne A, Cilluffo T, et al. Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H2-receptor antagonists. Gastroenterology 1985; 88:1842–1851.
12. Merki H, Witzel L, Harre K, et al. Circadian pattern of intragastric acidity in duodenal ulcer patients. A comparison with healthy controls. Gastroenterology 1986; 90:1549.
13. Merki H, Witzel L, Walt RP, et al. Day-to-day variation of 24-hour intragastric acidity. Gastroenterology 1988; 94:887–891.
14. Ritchie WP. Alkaline reflux gastritis: an objective assessment of its diagnosis and treatment. Ann Surg 1980; 92:288–298.
15. Bonavina L, Evander A, DeMeester TR, et al. Length of the distal esophageal sphincter and competency of the cardia. Am J Surg 1986; 151:25–34.
16. Lawson HH. Effect of duodenal contents on the gastric mucosa under experimental conditions. Lancet 1964; i:469–472.
17. Boren CH, Way LH. Alkaline reflux gastritis: a re-evaluation. Am J Surg 1980; 140:40–46.
18. Meshkinpour H, Marks JW, Schoenfield LJ, et al. Reflux gastritis syndrome: mechanism of symptoms. Gastroenterology 1980; 79;1283–1287.
19. Alexander-Williams J. Alkaline reflux gastritis: a myth or a disease? Am J Surg 1981; 143:17–21.
20. Keane FB, Dimagno EP, Malagelada JR. Duodenogastric reflux in humans: its relationship to fasting antroduodenal motility and gastric, pancreatic, and biliary secretion. Gastroenterology 1981; 81:726–731.
21. Keighley MRB, Asquith P, Alexander-Williams J. Duodenogastric reflux: a cause of gastric mucosal hyperaemia and symptoms after operations for peptic ulceration. Gut 1975; 16:28–32.
22. Hoare AM, Jones EL, Alexander-Williams J, Hawkins CF. Symptomatic significance of gastric mucosal changes after surgery for peptic ulcer. Gut 1977; 18:295–300.
23. Wickremesinghe PC, Dayrit PQ, Manfredi OL, et al. Quantitative evaluation of bile diversion surgery utilizing 99m Tc Hida scintigraphy. Gastroenterology 1983; 84:354–363.
24. Ritchie WP. Alkaline reflux gastritis: a critical reappraisal. Gut 1984; 25:975–987.
25. Boyle JM, Neiderhiser DH, Dworken HJ; Duodenogastric reflux in patients with gastric ulcer disease. J Lab Clin Med 1984; 103: 14–21.
26. Meyer JH. Reflections on reflux gastritis. Gastroenterology 1979; 77:1143–1145.
27. Ritchie WP Jr. Alkaline reflux gastritis: late results on a controlled trial of diagnosis and treatment. Ann Surg 1986; 203:537–544.
28. Warshaw AL. Intragastric alkali infusion: a simple, accurate provocative test for diagnosis of symptomatic alkaline reflux gastritis. Ann Surg 1981; 194:297–304.
29. Mackie CR, Wisbey ML, Cuschieri A. Milk $^{99}Tc^{M}$-EHIDA test for enterogastric bile reflux. Br J Surg 1982; 69:101–104.
30. Eyre-Brook IA, Holroyd AM, Johnson AG. Is bile reflux at endoscopy a significant finding? Scand J Gastroenterol 1984; 19(Suppl 92): 203–205.
31. Ludwig S, Ippoliti A. Objective evaluation of symptomatic alkaline reflux after antrectomy. Dig Dis Sci 1984; 29:824–828.
32. Schumpelick V. Duodenogastraler reflux—Faktum oder Fiktion? Dtsch Med Wschr 1984; 109:1205–1210.
33. DeMeester TR. The limitations of 24-hour pH monitoring of the esophagus. *In* DeMeester TR, Skinner DB, eds. Esophageal Disorders: Pathophysiology and Therapy. New York: Raven Press, 1985, pp 109–17.
34. Eyerly JB. Comparative pH values within the stomach, pylorus and duodenum in antacid treatment. Am J Dig Dis 1940; 7:431–434.
35. Rovelstad RA. Continuously recorded in situ pH of gastric and duodenal contents in patients with and without duodenal ulcers. Gastroenterology 1956; 31:530–537.
36. Etienne A, Fimmel CJ, Bron BA, et al. Evaluation of pirenzipine on gastric acidity in healty volunteers using ambulatory 24-hours intragastric pH-metry. Gut 1985; 26:241–245.
37. Little AG, Martinez EI, DeMeester TR, et al. Duodenogastric reflux and reflux esophagitis. Surgery 1984; 96:447–454.
38. DeMeester TR. Definition, detection, and pathophysiology of gastroesophageal reflux disease. *In* DeMeester TR, Matthews HR, eds. International Trends in General Thoracic Surgery, Volume III: Benign Esophageal Disease. St Louis: Mosby, 1987, pp 99–127.
39. Rinderknecht H. Pancreatic secretory enzymes. *In* Go VLW, Gardner JO, Brooks FP, Lebenthal E, DiMango EP, Scheele GA, eds. The Exocrine Pancreas: Biology, Pathobiology, and Diseases. New York: Raven Press, 1986, pp 163–83.
40. DeMeester TR, Fuchs KH, Ball CS, et al. Experimental and clinical results with proximal end-to-end duodenojejunostomy for pathologic duodenogastric reflux. Ann Surg 1987; 206:414–426.

# Cholangiocarcinoma Complicating Primary Sclerosing Cholangitis

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**Cholangiocarcinoma is more likely to develop in patients with primary sclerosing cholangitis. Our aims were to describe the clinical presentation, course, and management of patients afflicted with both cholangiocarcinoma and primary sclerosing cholangitis and to estimate the prevalence of cholangiocarcinoma in patients with primary sclerosing cholangitis. A retrospective analysis was conducted of 30 patients with both primary sclerosing cholangitis and cholangiocarcinoma managed at our institution during an 8-year period. Development of cholangiocarcinoma was heralded by rapid clinical deterioration with jaundice, weight loss, and abdominal discomfort. Cholangiocarcinoma complicating primary sclerosing cholangitis often was detected at an advanced tumor stage, which precluded effective therapy, and overall median survival was 5 months. Earlier recognition and treatment of cholangiocarcinoma in such patients will be necessary to increase survival rates. Seventy patients with primary sclerosing cholangitis were followed prospectively in a clinical trial of medical therapy for an average of 30 months. Twelve patients died and five were found at autopsy to have cholangiocarcinoma. The potential for cholangiocarcinoma to develop in patients with primary sclerosing cholangitis may indicate that liver transplantation should be considered earlier in the course of the disease.**

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PRIMARY SCLEROSING CHOLANGITIS (PSC) is a chronic cholestatic disease characterized by obliterative inflammatory fibrosis of the bile ducts. The disease is usually slowly progressive, refractory to medical therapy, and frequently leads to cirrhosis and death from liver failure. Recent clinical observations[1] and careful pathologic study[2] suggest that cholangiocarcinoma may arise in patients with pre-existing PSC. Many clinicians, however, have been skeptical of the concurrence of these two diseases. A diagnosis of PSC often is categorically excluded by suggestions that all cholangiographic and clinical findings of PSC in patients suspected of having both diseases are explicable by the presence of multicentric or diffuse ductal cholangiocarcinoma. However histologic or autopsy evidence substantiating such claims generally have been absent. In contrast our experience with PSC suggests that cholangiocarcinoma is associated with PSC and is not uncommon.

Thus we tried to define further the association between cholangiocarcinoma and PSC. Our aims were twofold: first to describe the clinical presentation, course, and management of patients afflicted with both PSC and cholangiocarcinoma; and second to estimate the prevalence of cholangiocarcinoma in patients with primary sclerosing cholangitis.

## Methods

We identified 30 patients evaluated at the Mayo Clinic between 1979 and 1987 with diagnoses of both primary sclerosing cholangitis and cholangiocarcinoma. A clinical diagnosis of PSC was supported by the following: classical radiographic features of PSC on cholangiography, elevation of the serum alkaline phosphatase to at least twice the upper limit of normal before cholangiocarcinoma development, and liver biopsy consistent with PSC. A diagnosis of cholangiocarcinoma required histologic or cytologic confirmation by biopsy or autopsy. Patient demographics, symptoms and signs, laboratory data, pathologic findings, operative management, and hospital morbidity and mortality were recorded for all patients. Follow-up was based on data abstracted from the clinical history. Patients still alive at the time of follow-up were evaluated clinically at the Mayo Clinic or were contacted by telephone or correspondence. Survival was calculated using the Kaplan–Meier product-limit method.[3]

To estimate the prevalence of cholangiocarcinoma associated with PSC, we evaluated all patients enrolled in

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a prospective clinical trial of medical therapy with D-Penicillamine (Merck Sharpe & Dohme, West Point, PA) for PSC.[4] Seventy patients were enrolled in the D-Penicillamine trial and the previously described diagnostic features of PSC were required for inclusion, with an additional requirement of established liver disease for more than 6 months' duration. Patients with intrahepatic cholangiographic abnormalities alone, cholangiographic changes highly suggestive of carcinoma, bile duct surgery or choledocholithiasis preceding the diagnosis of PSC, congenital bile duct abnormalities, a diagnosis of primary biliary cirrhosis, alcohol abuse, or a malignancy other than skin cancer were excluded. No patient was known to have cholangiocarcinoma when entered into the D-Penicillamine study. In each patient the diagnosis of cholangiocarcinoma was confirmed by biopsy or autopsy.

## Results

Thirty patients, 19 men and 11 women, with a mean age of 43 ± 10 years (range, 20 to 61 years) were found to have both PSC and cholangiocarcinoma at our institution between 1979 and 1987. This group of patients included five patients who were part of the D-Penicillamine trial. The diagnosis of PSC preceded the diagnosis of cholangiocarcinoma by a mean of 52 ± 43 months (range, 0 to 165 months) in 21 patients. Twelve patients had PSC for at least 2 years before diagnosis of cholangiocarcinoma. Synchronous diagnoses were made in nine patients.

Twenty-six patients (including all nine with synchronous diagnoses of PSC and cholangiocarcinoma) had classical radiographic features of PSC on cholangiography. Four patients did not have cholangiographic confirmation of PSC but each had long-standing liver disease with elevation of serum alkaline phosphatase for 4 to 7 years before diagnosis of cholangiocarcinoma. In addition each of these patients had chronic ulcerative colitis (CUC).

Twenty-five patients (83%) had inflammatory bowel disease. Twenty-four of these patients had CUC. The diagnosis of CUC preceded the diagnosis of PSC by a mean of 18 ± 11 years for 21 patients (range, 1 to 39 years) and followed the diagnosis of PSC by a mean of 4 ± 4 years for three patients (range, 1 to 8 years). One patient had undergone proctocolectomy for Crohn's colitis 22 years before PSC development.

### *Symptoms*

Twenty-three of thirty patients were alive when the diagnosis of cholangiocarcinoma was established. Symptoms at the time of diagnosis of cholangiocarcinoma are listed in Table 1. The most common symptoms were jaundice, weight loss, and abdominal discomfort.

Cholangiocarcinoma was detected before death for 10 of 12 patients for whom the diagnosis of PSC preceded that of carcinoma by at least 2 years. Jaundice developed rapidly in seven of these patients and was present 1 to 4 months before detection of carcinoma. Eight of these patients had weight loss of 7 to 32 pounds during the course of 1 to 6 months. During the interval between the diagnosis of PSC and cholangiocarcinoma, a twofold increase in serum alkaline phosphatase occurred in 7 of these 10 patients. No other laboratory values were found to change consistently during the interval between diagnoses.

TABLE 1. *Symptoms in Patients with PSC and Cholangiocarcinoma*

| Symptoms | *Patients (n = 23) |
|---|---|
| Jaundice | 18 |
| Weight loss | 16 |
| Abdominal discomfort | 14 |
| Pruritus | 12 |
| Fatigue/malaise | 12 |
| Fever | 8 |
| Anorexia | 4 |
| Gastrointestinal bleeding | 2 |

* Patients with diagnosis of cholangiocarcinoma at autopsy are excluded.

PSC, primary sclerosing cholangitis.

Twenty-one patients underwent operative or percutaneous liver biopsy at the time of diagnosis of cholangiocarcinoma. Histologic criteria for staging of PSC are cholangitis or portal hepatitis, stage I; periportal fibrosis or periportal hepatitis, stage II; septal fibrosis, bridging necrosis or both, stage III; and biliary cirrhosis, stage IV.[5] The extent of liver disease at the time of diagnosis of cholangiocarcinoma was stage I–1 (5%), stage II–8 (38%), stage III–6 (29%), and stage IV–6 (29%).

### *Diagnosis*

The diagnosis of cholangiocarcinoma was established operatively in 15 patients (2 during aborted orthotopic liver transplants when lymph node metastases were discovered) and nonoperatively by percutaneous needle biopsy in 6, by laparoscopy in 1, by biopsy of subcutaneous metastases in 1, and at autopsy in 7 (including the 5 patients in the D-Penicillamine study).

### *Location*

Cholangiocarcinomas arose intrahepatically in six patients and extrahepatically in 18 patients. The location of origin was indeterminate in six patients. The distribution of extrahepatic cholangiocarcinoma was primarily proximal, with six tumors arising at the hilus and four in the common hepatic duct. Four tumors arose in the common bile duct, and four tumors arose in the gallbladder or cystic duct. Three patients had clear evidence for multicentric cholangiocarcinoma: separate lesions in remote locations confirmed by biopsy.

### *Metastases*

Nineteen patients (63%) had metastatic disease present at the time of diagnosis of cholangiocarcinoma. Fourteen patients (47%) had intra-abdominal metastases only, and five patients (16%) had both intra- and extra-abdominal disease. Locations of metastases are listed in Table 2.

Seventeen patients underwent abdominal exploration (two subsequent to percutaneous biopsy) and eight patients were found to have intra-abdominal metastatic disease. Six patients had involvement of regional (choledochal, hepatic artery, and celiac trunk) lymph nodes; one had multiple hepatic metastases, and one had peritoneal carcinomatosis.

### *Treatment and Survival*

Overall median survival was 5 months following the diagnosis of cholangiocarcinoma, excluding seven patients with autopsy diagnosis and two patients lost to follow-up (Fig. 1). Survival with respect to treatment is depicted in Figure 2.

Only one patient underwent potentially curative resection. This 32-year-old woman had a cholangiocarcinoma in the common bile duct and is alive and free of disease 26 months after pancreatoduodenectomy. She had no regional lymph node involvement.

Seven patients (one lost to follow-up) underwent palliative resection. Resection was incomplete due to involvement of the bile duct at the margin of resection in five patients. One patient with regional lymph node involvement underwent palliative left lateral hepatectomy and is alive after 2 months. The remaining patient had multifocal disease with low-grade carcinoma present in the distal common bile duct and right hepatic duct. A palliative resection of the distal common bile duct lesion was performed, but the patient had advanced cirrhosis and died from gastrointestinal hemorrhage 3 months later. Median survival after palliative resection was 10 months.

TABLE 2. *Site of Metastases Present at Time of Diagnosis of Cholangiocarcinoma in Patients with PSC and Cholangiocarcinoma*

| Site | No. of Patients |
|---|---|
| Regional lymph nodes | 13 |
| Liver | 7 |
| Lung | 2 |
| Skin | 2 |
| Peritoneum | 1 |
| Bone | 1 |

PSC, primary sclerosing cholangitis.

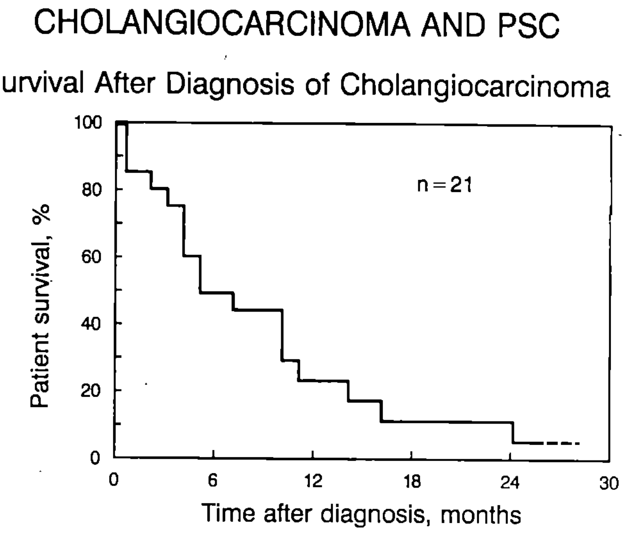

FIG. 1. Survival after diagnosis of cholangiocarcinoma.

Four patients received radiotherapy after palliative resection. One was lost to follow-up and the others survived 7, 10, and 16 months.

Nine patients had palliation of bile duct obstruction by intubation techniques (operative, endoscopic, and percutaneous) and had a median survival time of 5 months. Two patients received external beam radiation therapy; one survived 14 months, and the other is alive after 1 month. One patient received intraoperative and external beam radiotherapy and survived 24 months.

Six patients (one lost to follow-up) had advanced disease that was not amenable to operative palliation or intubation. They had a median survival of 4 months. Two received radiotherapy and survived 4 and 10 months.

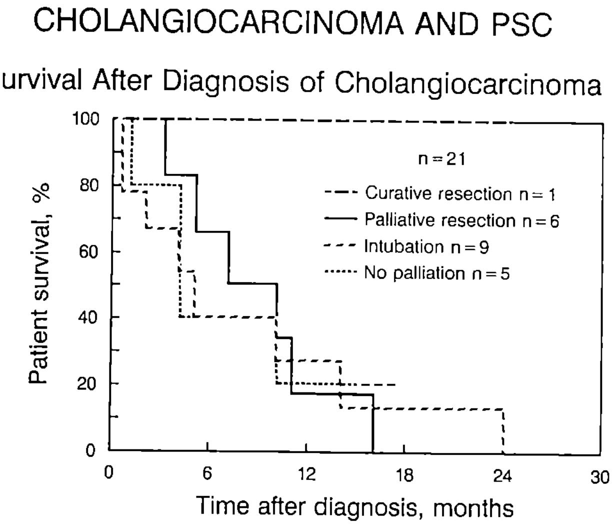

FIG. 2. Survival after diagnosis of cholangiocarcinoma by treatment modality.

*Prevalence*

Seventy patients with PSC were followed prospectively for a mean of 30 months in a randomized trial of medical therapy with D-Penicillamine. During this period, 15 patients died. All died with liver failure and 12 had autopsies. Cholangiocarcinoma was found at autopsy in five of these cases. No patient in the study had a diagnosis of cholangiocarcinoma made while alive. Thus cholangiocarcinoma occurred in at least 7% (5 of 70) of the patients in the study and in 42% (5 of 12) of the autopsied patients. All five patients with cholangiocarcinoma had advanced PSC with cirrhosis and portal hypertension at the time of death and all five patients had long-standing chronic ulcerative colitis (mean duration, 20 years). Patients with cholangiocarcinoma and PSC tended to be older (mean, 50 *versus* 38 years, $p = 0.06$, two-tailed t test) and tended to have had chronic ulcerative colitis longer (mean, 20 *versus* 8 years, $p = 0.05$, two-tailed t test) than patients with PSC alone. Other clinical and biochemical information did not distinguish in which patients cholangiocarcinoma would be more or less likely to develop.

## Discussion

The results of our study suggest an association between PSC and cholangiocarcinoma. Cholangiocarcinoma frequently arose in patients with PSC and was heralded by rapid clinical deterioration with progressive jaundice, weight loss, and pain. Cholangiocarcinoma occurring in the setting of PSC was nearly always detected at an advanced stage that precluded potentially curative resection. Therapeutic options were limited and survival was short.

Many clinicians have considered concurrent diagnoses of PSC and cholangiocarcinoma to be mutually exclusive. This attitude is based on the premise that the characteristic cholangiographic and clinical features of PSC are explicable by the presence of diffuse infiltrating ductal cholangiocarcinoma. However there is little evidence to support this premise. Cholangiocarcinoma is, indeed, capable of extensive periductal infiltration but spread of tumor is usually radial from its origin and is limited radially to 5 cm.[6] Diffuse cholangiocarcinoma, which can masquerade as PSC with a similar extrahepatic and intrahepatic radiographic appearance, is distinctly uncommon. Extensive periductal infiltration was present in only 4 of 22 patients with sclerosing cholangiocarcinoma in the series reported by Weinbren and Mutum.[6] Furthermore long-term survival after onset of symptoms of hepatobiliary disease, extending for 20 years in some of our patients, is inconsistent with our knowledge of the natural history of cholangiocarcinoma with an expected survival range of 6 to 12 months for most patients after diagnosis.[7] Clearly cholangiocarcinoma that is cholangiographically similar to PSC represents an advanced stage with an expected short survival time and, therefore, categorically excluding the diagnosis of PSC is inconsistent with these findings.

Conversely there is pathologic evidence that cholangiocarcinoma may arise in the setting of PSC. Wee et al.[2] demonstrated histologic changes of PSC distant from malignant areas and the presence of carcinoma *in situ* in areas with fibrous cholangitis in patients with long-standing hepatobiliary disease and CUC. The relationship between cholangiocarcinoma and chronic ulcerative colitis (CUC) is well known. Studies by Ritchie et al.[8] and Akwari et al.[9] demonstrated that the incidence of cholangiocarcinoma in patients with CUC far exceeded that in the general population. Furthermore a recent study from the Cleveland Clinic estimated that the relative risk of cholangiocarcinoma developing in patients with CUC was 31.3 times greater than the risk to the general population.[1] We believe that this increased risk is due to the concomitant presence of PSC. Indeed, in the study by Wee et al.,[2] which re-examined the patients studied by Akwari et al.,[9] cholangiocarcinoma was never found in the absence of PSC.

We found that cholangiocarcinoma was present in at least 7% (5 of 70) of the patients and 42% of the autopsied patients with PSC followed prospectively for an average of 30 months. Although surprisingly high, these figures probably underestimate the true incidence of cholangiocarcinoma in patients with PSC. Because cholangiocarcinomas in the D-Penicillamine study were found only at autopsy, it is possible that additional tumors remain undetected.

Although our estimate of prevalence may have been influenced by a referral bias to our tertiary care center, other studies also have recognized a similar prevalence of cholangiocarcinoma arising in patients with PSC. Chapman et al.[10] reviewed 29 patients with PSC. Eleven of these patients died with a mean survival of 7 years from the time of diagnosis, and three were found to have cholangiocarcinoma. Similarly Aadlund et al.[11] reported cholangiocarcinoma in 4 of 45 patients (8.9%) with PSC. All were found at autopsy with a frequency of 33% (12 autopsies). Marsh et al.[12] recently reported the University of Pittsburgh experience with orthotopic liver transplantation for PSC. Five of fifty-five patients (9%) were found to have previously unrecognized cholangiocarcinoma at the time of transplantation. This prevalence of cholangiocarcinoma in patients with PSC is strikingly similar to our own.

We fully recognize that the clinical distinction between patients with both PSC and cholangiocarcinoma and those with PSC alone is often difficult. Although jaundice, weight loss, and abdominal discomfort were present in 75%, 70%, and 61% of the patients with both diseases, these symptoms are not specific and occur in a similar proportion of patients with PSC alone.[10,13] Our impression, however, is that cholangiocarcinoma in patients with PSC may be heralded by more rapid clinical and biochemical deterioration than we have seen with PSC alone. Increasing jaundice and decreasing clinical performance status often prompted hepatobiliary imaging, which led to intervention and diagnosis in some of our patients.

We could not identify any laboratory features that reliably indicated the presence of cholangiocarcinoma in patients with PSC. Serum alkaline phosphatase tended to increase during the interval between the diagnosis of PSC and cholangiocarcinoma when an interval existed, but this change was not consistent. Similarly the histologic stage of PSC did not correlate patients with cholangiocarcinoma. The distribution of cholangiocarcinoma between stage II, III, and IV disease was nearly equal. Lack of correlation to the stage of PSC is not surprising given the variable natural history of PSC.[13]

The prognosis for patients with PSC and cholangiocarcinoma is poor. Median survival was only 7 months following the diagnosis of cholangiocarcinoma. Survival was short because of the advanced stage of cholangiocarcinoma at the time of diagnosis. Metastatic disease was common and was present in 63% of the patients at the time of diagnosis. Metastases or local extent of disease precluded potentially curative resection in all but one patient.

Clearly there is a need for earlier detection and effective therapy for patients in whom cholangiocarcinoma develops in the setting of PSC. Operative resection may be effective in few patients. Delayed diagnosis, tumor multicentricity, and advanced stage of disease frequently preclude potentially curative resection. Earlier diagnosis aided by screening or heightened clinical awareness could improve the effectiveness of operative resection. However survival rates may remain poor due to the natural history of PSC, and operative intervention has not been shown to retard the clinical progression of PSC.

Orthotopic liver transplantation is the only therapeutic alternative that offers both radical eradication of tumor and a potential cure for PSC. However recurrent disease developed within 1 year in three of five patients who underwent liver transplantation for both PSC and cholangiocarcinoma in the University of Pittsburgh experience.[12] Thus until we are better able to detect cholangiocarcinoma arising in the setting of PSC or to predict its development, it may be better to offer liver transplantation earlier for patients with PSC. Whereas the indications for liver transplantation now are based on clinical criteria for patients with PSC, the potential for cholangiocarcinoma to develop may now be an indication for considering earlier intervention.

We believe an association clearly exists between PSC and cholangiocarcinoma. We wonder whether the chronic inflammatory process of PSC predisposes bile duct epithelium to malignant transformation. The association of chronic inflammation and gastrointestinal carcinoma is not unique. Chronic inflammation caused by cholelithiasis[14] and *Clonorchis sinensis*[15] have been associated with carcinoma of the gallbladder and bile ducts, respectively. Because PSC so often occurs in patients with CUC, we wonder whether similar mechanisms of carcinogenesis for colon cancer with CUC and bile duct cancer with PSC exist. Further studies are needed to define the association between PSC and cholangiocarcinoma and to determine if PSC is a premalignant condition.

## References

1. Mir-Madjlessi SH, Farmer RG, Sivak MV. Bile duct carcinoma in patients with ulcerative colitis. Dig Dis Sci 1987; 32:145–154.
2. Wee A, Ludwig J, Coffey RJ, et al. Hepatobiliary carcinoma associated with primary sclerosing cholangitis and chronic ulcerative colitis. Hum Pathol 1985; 16:719–726.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. JASA 1958; 53:457–481.
4. LaRusso NF, Wiesner RH, Ludwig J, et al. A prospective trial of Penicillamine in primary sclerosing cholangitis. Gastroenterology 1988; 95:1036–1042.
5. Ludwig J, Barham SS, LaRusso NF, et al. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis or chronic ulcerative colitis. Hepatology 1981; 1:632–640.
6. Weinbren K, Mutum SS. Pathological aspects of cholangiocarcinoma. J Pathol 1983; 139:217–238.
7. Blumgart LH. Cancer of the bile ducts. *In* Blumgart LH, ed. Surgery of the Liver and Biliary Tract. Edinburgh, UK: Churchill Livingstone, 1988, pp 829–853.
8. Ritchie JK, Allan RN, Macartney J, et al. Biliary tract carcinoma associated with ulcerative colitis. Q J Med 1974; 43:263–279.
9. Akwari OE, van Heerden JA, Foulk WT, Baggenstoss AH. Cancer of the bile ducts associated with ulcerative colitis. Ann Surg 1975; 181:303–309.
10. Chapman RWG, Marborgh BA, Rhodes JM, et al. Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. Gut 1980; 21:870–877.
11. Aadlund E, Schrumpf E, Fousa O, et al. Primary sclerosing cholangitis: a long-term followup study. Scand J Gastroenterol 1987; 22:655–664.
12. Marsh JW, Iwatsuki S, Makowka L, et al. Orthotopic liver transplantation for primary sclerosing cholangitis. Ann Surg 1988; 207:21–25.
13. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology 1980; 79:200–206.
14. Talbet BJ. Primary carcinoma of the gallbladder. Am J Surg 1960; 100:363–371.
15. Belmaric J. Intrahepatic bile duct carcinoma and Clonorchis sinensis infection in Hong Kong. Cancer 1973; 31:468–473.

# Elevated Circulating Interleukin-6 Is Associated with an Acute-phase Response but Reduced Fixed Hepatic Protein Synthesis in Patients with Cancer

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**It has been suggested that, as part of the inflammatory response to the presence of a tumor, various cytokines are produced and these induce hepatic synthesis of acute-phase proteins (APP). Under these circumstances it is not known what changes occur in the fixed component of hepatic protein synthesis. The aim of this study was to compare circulating interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) concentrations and fixed hepatic protein synthesis rates in a group of healthy controls ($n = 6$) with a group of patients with an established APP response secondary to hepatic metastasis from colorectal cancer ($n = 6$). Fixed hepatic protein synthesis rates were measured following a primed, constant 20-hour infusion of $^{15}$N-glycine. The liver was biopsied at laparotomy. The APP response was assessed by serum C-reactive protein concentration and cytokines were assayed by a combination of immunoassay and bioassay. The patients with advanced cancer and an on-going APP response had elevated circulating IL-6 concentrations ($p < 0.01$). Rates of fixed hepatic protein synthesis were 30% lower than those observed in controls ($p < 0.01$). These findings demonstrate that in patients with hepatic metastasis, although the synthesis of certain acute-phase export proteins can be increased, fixed protein synthesis is reduced. Whether these changes in the distribution of hepatic protein synthesis are mediated by IL-6 will require further investigation.**

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MOST CANCER PATIENTS with progressive disease lose weight and some become so emaciated that they appear to die primarily from cachexia.[1,2] The mechanisms that underlie this complex syndrome of nutritional and metabolic upset are understood poorly.[3,4] One observation that has been made repeatedly is that a proportion of cancer patients with weight loss appear to have inappropriately elevated rates of whole-body protein turnover.[5-8] Such increased protein turnover might compromise the normal adaptation to semistarvation and contribute to the accelerated weight loss of the cachectic cancer patient.[6] However it is not known which tissues in the body contribute to this elevated protein flux and the factors that may mediate these changes have not been identified.

The normal liver is known to have a major synthetic capacity that is divided between the production of export and fixed proteins and which, in mammals, accounts for up to 15% of total-body protein synthesis.[9] The circulating concentration of certain hepatic export proteins (*e.g.*, acute-phase proteins) has been shown to be increased in patients with advanced malignancy[10,11] and therefore it has been suggested that the liver may be one of the organs that contributes to the accelerated protein synthesis observed in emaciated cancer patients.[6] In support of the concept that hepatic protein synthesis may be accelerated in the cancer host, various studies of body composition and organ volumes in cachectic cancer patients suggest that in distinction to other viscera, liver mass tends to be preserved or even increased.[12,13] Clearly the mass of protein in an organ is determined by the balance between synthesis and degradation. If the increased hepatic mass of cancer patients were principally the result of enhanced protein synthesis rather than reduced degradation, then this could mean that both export and fixed protein synthesis is increased. However there have been no direct measurements of fixed hepatic protein synthesis in patients with cancer.

Many hypotheses have been proposed to account for the way in which a tumor might influence host protein metabolism. Most recently it was suggested that as part

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of the inflammatory response to the presence of a tumor, a variety of cytokines are produced and the diverse metabolic effects of these peptides may account for many of the changes in the metabolism of protein, energy, and trace element metabolism observed in the cachectic cancer patient.[14] The presence of an inflammatory response may be documented by the appearance of acute-phase proteins in a patient's serum[15] and indeed most cancer patients with progressive disease develop such a response.[10,11] Cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) have been shown both *in vitro*[16–18] and *in vivo*[19,20] to elicit acute-phase protein production. However, although these cytokines may increase the rate of synthesis of such hepatic export proteins, it is not known what effect they have on the rate of fixed hepatic protein synthesis.

We demonstrated previously that patients with hepatic mestastasis from colorectal cancer tend to have an acute-phase response and accelerated whole-body protein kinetics.[5] The aim of the present study was to investigate the relationship between cytokine production, the acute-phase response, and the rate of hepatic fixed protein synthesis in such patients. Whole-body and fixed hepatic protein synthesis rates were measured in six colon cancer patients with known hepatic metastasis and an on-going acute-phase protein response, and in six weight stable, noncancer patients with no acute-phase response. The potential role of IL-1, IL-6, and TNF in mediating changes in the protein metabolism of the cancer patients was addressed by measuring the serum concentration of these cytokines in both groups.

## Materials and Methods

### *Patients*

Six patients with histologically proved colonic adenocarcinoma and multiple hepatic metastasis who had not undergone surgery within the previous 3 months and who had evidence of an acute-phase protein response (serum C-reactive protein concentration more than 10 mg/L) were entered into the study. Both lobes of the liver were involved in all patients; however, at the time of laparotomy, there was no clinical or radiologic evidence of extrahepatic spread. These patients had been admitted to undergo insertion of an implantable injection system for administration of chemotherapy *via* the hepatic artery. Six patients with cholelithiasis whose last clinical attack had been at least 3 months earlier, with no history of jaundice, and normal liver function tests were entered as controls. These patients were weight stable, had no evidence of an acute-phase response, and had been admitted for elective cholecystectomy. All individuals were of performance status 2 or better (WHO Performance Score) and were clinically judged to be free of other metabolic or endocrine disorders. None were pyrexial, had clinical or radiologic evidence of infection, were receiving steroids, or were severely anemic. All patients had a normal serum urea and creatinine concentration and although some patients with hepatic metastasis had abnormal liver function tests, none were clinically jaundiced (serum bilirubin less than 35 $\mu$mol/L)

The study was approved by the local ethical committee. All patients were informed of the purpose and procedures of the study and all gave written, informed consent.

### *Experimental Design*

Following a 12-hour fast, a spot urine sample was collected for baseline enrichment measurement of urinary ammonia, and a venous blood sample was taken for measurement of serum IL-1, IL-6, TNF, and C-reactive protein concentration. A primed (0.06 mg/kg) constant, 20-hour intravenous infusion (0.06 mg/kg/hr) of $^{15}$N-glycine (99 atom %, Tracer Technologies Inc., Somerville, MA) then was commenced. All voided urine was collected for the next 18 hours and analyzed for nitrogen content by the microkjeldahl method.[21] Immediately before surgery (20 hours), a urine sample was obtained for measurement of plateau $^{15}$N enrichment of urinary ammonia. Within 10 minutes of the start of the operation, a wedge liver biopsy was taken, rapidly frozen, and from this biopsy $^{15}$N-glycine enrichment in the intracellular free amino acids and protein hydrolysate was measured.

### *Analytical Methods*

*Urine sample preparation.* Ammonia was extracted from the urine with an ion exchange resin[22] and analyzed for $^{15}$N by continuous flow isotope ratio mass spectrometry (CF-IRMS).[23]

*Tissue sample preparation.* The liver was homogenized in 0.2 mol/L (molar) HCl and then centrifuged at 1000*g* for 35 minutes to yield soluble and nonsoluble material. The soluble material was deproteinized by further centrifugation at 1000*g* for 35 minutes through an ultrafiltration cone (Amicon, Stonehouse, UK). The amino acids were purified further with a cation exchange resin ($H^+$ form) and then reconstituted in 0.2 mol/L pyridine formate at pH 2.1 before injection into the high-performance liquid chromatography (HPLC) cation exchange column.

The nonsoluble fraction (incorporated glycine) was hydrolyzed in 6 mol/L HCl at 145 C under vacuum for 4 hours. The HCl was removed by vacuum distillation and followed by an ion exchange purification (see above). After HPLC separation isotope analysis of glycine from the protein hydrolysate and free amino acids was carried out by CF-IRMS.

*Amino acid separation by HPLC.* A 50-$\mu$l aliquot of reconstituted amino acid solution was injected onto a 250

× 4.6 mm cation exchange column (Amino acid analysis column AA911 packed with a sulphonated polysterene-divinyl-benzene copolymer; Interaction Chemicals Inc., Mountain View, CA). The amino acids were eluted with 0.2 mol/L pyridine formate, pH 3.1 at 50 C and a flow rate of 0.4 mL/minute. This buffer system gave optimal separation of the neutral aminoacids, although only glycine fractions were collected. Retention time and peak shape of glycine was determined using 14 C labeled glycine. An ultraviolet detector at 278 nm was used to monitor retention times and amino acid separation from sample to sample. The glycine peak was collected in 10 × 280 $\mu$L fractions and freeze dried before CF-IRMS analysis.

*$^{15}$N analysis by CF-IRMS.* Continuous flow isotope ratio mass spectrometry was carried out on an automated nitrogen analyzer interfaced to a dual collector isotope ratio mass spectrometer, as described previously.[23]

*Cytokine assays.* Serum tumor necrosis factor (IRE-Medgenix, Fleurus, Belgium) and IL-1B (Cistron, Pine Brook, NJ) were determined by immunoassay. The limits of detection for TNF were 12 pg/mL and 20 pg/ml for IL-1B. Chloroform extraction of serum was undertaken before assay for IL-1B.[24] Interleukin-6 was determined by bioassay using 7TD1 cells.[25] The specificity of the assay was demonstrated by inhibition of all stimulatory activity with the use of a polyclonal antiserum to IL-6 (gift of Dr. J. Van Damme). The limit of detection for IL-6 was approximately 10 U/mL. The assay was calibrated using recombinant IL-6 (gift of Dr. L. Aarden), and 1 unit is approximately equivalent to 1 pg of IL-6.

*Assessment of acute-phase protein status.* Serum C-reactive protein was measured in all patients as a marker for the presence of an acute-phase response.[15] Serum taken before the protein synthesis study was stored at −80 C until analysis. C-reactive protein was measured by a fluorescence polarization immunoassay (Abbott T D X, Maidenhead, UK). A concentration of more than 10 mg/L was designated as a positive acute-phase response.

### *Calculations*

Rates of whole-body protein turnover were calculated using the stochastic model of Picou and Taylor-Roberts.[26] The basic assumption of this model is that in the steady state and at isotopic equilibrium the proportion of isotope excreted in the chosen end product of nitrogen metabolism (ammonia) is the same as the proportion of the nitrogen turnover excreted in that same end product. Nitrogen turnover was calculated using the formula $Q = d/e$, where Q is nitrogen turnover, d the quantity of isotope infused, and e the isotopic enrichment of the chosen urinary end product.

The assumptions of the stochastic model mean that in the steady state Q is equal to the rate of protein synthesis (S) plus the rate of nitrogen excretion (E). This rate of synthesis also equals the rate of protein breakdown (B) plus the rate of nitrogen intake (I). Thus $Q = I + B = S + E$. Because this study was performed with patients in the fasting state, the rate of protein turnover is equal to the rate of protein breakdown. Rates of whole-body protein synthesis were calculated by subtracting 24-hour urinary nitrogen excretion from Q.

The fractional synthesis rate for hepatic protein synthesis was obtained by dividing the protein enrichment by the precursor enrichment of $^{15}$N-glycine and multiplying by 100 to give a percentage figure.[27] The free glycine enrichment obtained from the liver homogenate was assumed to be the same as that in the true precursor pool.

### *Statistical Analysis*

All group data is presented as the mean ± SEM. Except where stated, statistical significance was ascertained using the Mann–Whitney U test.

## Results

The clinical features of the cancer patients and controls are shown in Table 1. In contrast to the weight-stable controls, the cancer patients lost on average 10% of their pre-illness stable weight during a mean period of 4 months. The mean serum albumin concentration of the cancer patients was less than the normal range (36 to 44 g/L) and significantly lower than that of the controls (34 ± 2 *versus* 41 ± 1 g/L; $p < 0.01$).

Individual rates of whole-body protein synthesis, whole-body protein breakdown, fixed hepatic protein synthesis, and urinary nitrogen excretion of the cancer patients and

TABLE 1. *Patient Characteristics*

| Subjects | Age (yrs) | Sex | Weight (kg) | Weight Loss (%) | Albumin (g/L) |
|---|---|---|---|---|---|
| Control | | | | | |
| 1 | 70 | F | 74 | — | 40 |
| 2 | 53 | F | 69 | — | 40 |
| 3 | 74 | F | 60 | — | 39 |
| 4 | 67 | F | 70 | — | 43 |
| 5 | 58 | F | 58 | — | 41 |
| 6 | 39 | F | 86 | — | 41 |
| Mean | 60 | | 70 | | 41 |
| SEM | 5 | | 4 | | 1 |
| Cancer | | | | | |
| 1 | 54 | M | 63 | 19 | 34 |
| 2 | 78 | F | 52 | 15 | 24 |
| 3 | 59 | M | 67 | 7 | 39 |
| 4 | 42 | M | 77 | 8 | 35 |
| 5 | 68 | M | 72 | 6 | 39 |
| 6 | 62 | M | 65 | 7 | 31 |
| Mean | 61 | | 66 | 10 | 34* |
| SEM | 5 | | 3 | 2 | 2 |

* $p < 0.01$.

controls are presented in Table 2. The mean rate of whole-body protein synthesis in the cancer patients was 71% greater than that of the controls ($p < 0.05$). Similarly whole-body protein breakdown was 69% greater in the cancer patients compared with the controls ($p < 0.05$). For individual patients, the rates of protein breakdown were all greater than the corresponding rates of protein synthesis because measurements were made with the subjects in the postabsorptive state.

Mean rates of whole-body protein breakdown exceeded those of whole-body protein synthesis rates by 0.6 gP/kg/day in cancer patients and by 0.4 gP/kg/day in the controls. This greater protein loss in the cancer patients reflected the higher rates of urinary nitrogen excretion in the cancer patients than in controls (6.1 ± 1.5 *versus* 4.2 ± 0.9 gN/day). However this difference was not statistically significant. In contrast to whole-body rates, the mean fixed hepatic protein fractional synthetic rate was 30% lower in the cancer patients than in controls ($p < 0.01$).

The serum concentrations of C-reactive protein, IL-1, IL-6, and TNF in the cancer patients and controls are shown in Table 3. An acute-phase protein response (C-reactive protein more than 10 mg/L) was present in all of the cancer patients but was not detected in any of the controls. The serum IL-6 concentrations in the cancer patients (range, 26 to 330 U/mL) were significantly greater than those of the controls (range, less than 10 to 16 U/mL, $p < 0.01$). Three of the six cancer patients had detectable serum concentrations of TNF compared with none of the controls. However this difference was not statistically significant (Fisher's Exact Test, $p > 0.1$). Interleukin-1 was not detected in the serum of either group.

TABLE 2. *Protein Kinetics and Urinary Nitrogen Excretion of Cancer Patients and Controls*

| Subjects | WBPS (gP/kg/d) | WBPB (gP/kg/d) | Urinary N (gN/d)‡ | HFSR (%/d) |
|---|---|---|---|---|
| Control | | | | |
| 1 | 3.3 | 3.5 | 2.6 | 10.9 |
| 2 | 2.4 | 2.9 | 4.8 | 10.5 |
| 3 | 5.1 | 5.4 | 3.1 | 10.8 |
| 4 | 2.6 | 2.9 | 3.6 | 11.1 |
| 5 | 2.0 | 2.3 | 2.7 | 11.1 |
| 6 | 3.4 | 4.0 | 8.1 | 10.6 |
| Mean | 3.1 | 3.5 | 4.2 | 10.8 |
| SEM | 0.4 | 0.4 | 0.9 | 0.1 |
| Cancer | | | | |
| 1 | 5.0 | 5.4 | 3.7 | 7.8 |
| 2 | 7.3 | 7.4 | 1.4 | 9.5 |
| 3 | 2.8 | 3.5 | 8.4 | 8.0 |
| 4 | 5.0 | 5.6 | 7.5 | 9.8 |
| 5 | 5.3 | 5.6 | 4.0 | 6.2 |
| 6 | 6.5 | 7.6 | 11.3 | 4.0 |
| Mean | 5.3* | 5.9* | 6.1 | 7.6† |
| SEM | 0.6 | 0.6 | 1.5 | 0.8 |

* $p < 0.05$; †$p < 0.01$; ‡Values calculated from 18-hour collection. (See Materials and Methods).

WBPB, Whole-body protein breakdown; WBPS, whole-body protein synthesis; HFSR, hepatic fractional synthetic rate.

TABLE 3. *Serum Acute-phase and Cytokine Responses of Cancer Patients and Controls*

| Subjects | C-reactive Protein (mg/L) | Il-6 (U/mL) | TNF (pg/mL) | Il-1 (pg/mL) |
|---|---|---|---|---|
| Control | | | | |
| 1 | 10 | 16 | <12 | <20 |
| 2 | 10 | 10 | <12 | <20 |
| 3 | 6 | <10 | <12 | <20 |
| 4 | 10 | <10 | <12 | <20 |
| 5 | 8 | 14 | <12 | <20 |
| 6 | 8 | 13 | <12 | <20 |
| Mean | 9 | | | |
| SEM | 1 | | | |
| Cancer | | | | |
| 1 | 120 | 330 | 15 | <20 |
| 2 | 41 | 96 | 22 | <20 |
| 3 | 11 | 26 | <12 | <20 |
| 4 | 115 | 170 | <12 | <20 |
| 5 | 52 | 70 | <12 | <20 |
| 6 | 108 | 118 | 15 | <20 |
| Mean | 75* | | | |
| SEM | 19 | | | |

* $p < 0.05$.

## Discussion

We demonstrated that patients with hepatic metastasis secondary to colon cancer have rates of whole-body protein synthesis that are 70% greater than those observed in noncancer controls (Table 2). These results are consistent with our previous findings[5] and correlate with those of other investigators who have observed increased whole-body protein synthesis in patients with advanced malignancy.[6,7] In contrast to the whole-body measurements, fixed hepatic protein synthesis in the cancer patients was reduced by 30% (Table 2). This clearly excludes accelerated synthesis of structural hepatic proteins as a factor that might contribute to the increased synthesis noted in the whole body. Furthermore these results suggest that any increase in hepatic protein mass associated with malignancy[12] is likely to be the outcome of decreased protein degradation rather than increased synthesis.

Our observations represent the first *in vivo* measurements of hepatic fixed protein synthesis in cancer patients and therefore it is impossible to compare our findings with other studies in humans. With reference to various animal models, our findings are consistent with those of Emery and coworkers,[28] who demonstrated a reduction in protein synthesis in the liver of thymectomized mice bearing the XK1 tumor. This is an important model of human cancer cachexia because the XK1 tumor is human in origin and induces weight loss when tumor mass is similar to that at which weight loss occurs in humans (*i.e.*,

<5% total-body weight[29]). In contrast. Pain and coworkers[30] reported increased total hepatic protein synthesis in mice bearing rodent ascites tumors. However in this model the tumor mass accounted for 60% of total-body weight and the situation cannot be compared with that which pertains in humans. Lundholm and coworkers[31] reported an increased incorporation rate of amino acids into hepatic proteins in sarcoma-bearing mice as well as in liver tissue from cancer patients. However the latter study involved using isolated tissue samples incubated *in vitro*, and the results obtained may not be physiologically meaningful. Furthermore the *in vivo* mouse studies were limited to measurements of incorporation of radioactively labeled amino acids into protein, without consideration of the precursor pool-specific activity, so the absolute rates of protein synthesis could not be calculated. Therefore it is apparent that the results of hepatic protein metabolism studies in cancer can vary according to the model selected and any conclusions may be limited by methodologic considerations.

Several investigators reported reduced rates of protein synthesis in the skeletal muscle of humans[32] and animals[28] with cancer cachexia. In this study we report reduced synthesis of fixed proteins in the liver and yet whole-body protein synthesis was increased. These observations on tissue-specific rates of protein synthesis suggest that there may be compartmentation of the tracer in the whole-body tracer studies and that certain organs or tissues may unduly influence the results. The exact relationship between kinetic parameters measured by tracer amino acid infusion and body protein kinetics remains unclear. However it is possible that this problem might be resolved in the future by measurement of tissue-specific protein synthesis rates in the other tissues of the body.

We examined a homogenous group of patients with hepatic metastasis from colon cancer. The patients, therefore, had similar tumor type and burden. Furthermore, to avoid any confounding metabolic factors associated with severe cachexia or malnutrition, patients were studied when they had, on average, lost 10% of their pre-illness weight (Table 1). A primed, constant infusion of $^{15}$N-glycine was used to allow simultaneous measurement of whole-body nitrogen kinetics and hepatic fractional protein synthesis rates. In the calculation of the latter, $^{15}$N-glycine enrichment in the precursor pool for protein synthesis was assumed to be at a constant level throughout the 20 hours of infusion. Obviously ethical considerations preclude repeated liver biopsy and therefore we were not able to check this assumption directly. Nevertheless, using the same prime to infusion ratio, it was shown previously that the free plasma glycine pool reaches plateau in about 15 minutes and urinary hippurate, used as an indirect measure of free hepatic glycine, reaches 95% of plateau enrichment within 1 hour.[33] The duration of infusion that we used (20 hours) indicates that any error introduced by variation in the time to plateau isotopic enrichment would be minimal.

One cause of an increased rate of whole-body protein synthesis in cancer patients might be the production of inflammatory mediators in response to neoplasia. Elevated circulating levels of TNF[34] and Il-6[35] have been detected in the serum of tumor-bearing rodents. In this study we report significantly elevated circulating Il-6 concentrations in advanced cancer patients compared with controls (Table 3). Because Il-6 is known to elicit acute-phase protein production both *in vitro*[18] and *in vivo*,[20] potentially this polypeptide could have induced the acute-phase protein response observed in the cancer patients (Table 3). In addition, there is evidence from hepatocyte-Kupffer cell coculture systems that suggests that stimuli for cytokine production (such as endotoxin) may reduce overall protein synthesis in the hepatocyte. Therefore it is possible that the observed reduction in fixed hepatic protein synthesis (Table 2) was also cytokine mediated. Whether the simultaneous increase in acute-phase protein production but decrease in fixed protein synthesis represents a basic mechanism of nitrogen economy in the liver requires further investigation. However, if these effects are mediated by the same agent, then this might provide a key target for future manipulation of hepatic protein metabolism not only in cancer but also in a variety of other disease states.

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## References

1. Warren S. The immediate causes of death in cancer. Am J Med Sci 1932; 184:610–616.
2. Inagaki J, Rodriguez V, Bodey GP. Causes of death in cancer patients. Cancer 1974; 33:568–573.
3. Calman KC. Cancer cachexia. Br J Hosp Med 1982; 26:28–34.
4. Fearon KCH, Carter DC. Cancer cachexia. Ann Surg 1988; 208:1–5.
5. Fearon KCH, Hansell DT, Preston T, et al. Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer. Cancer Res 1988; 48:2590–2959.
6. Eden E, Ekman L, Bennegard K, et al. Whole body tyrosine flux in relation to energy expenditure in weight-losing cancer patients. Metabolism 1984; 33:1020–1027.
7. Jeevanandam M, Lowry SF, Horowitz GD, Brennan MF. Cancer cachexia and protein metabolism. Lancet 1984; i:1423–1426.
8. Inculet RI, Stein P, Peacock JL, et al. Altered leucine metabolism in non-cachectic sarcoma patients. Cancer Res 1987; 47:4746–4749.
9. Attaix D, Aurousseay E, Manghebati A, Arnal M. Contribution of liver, skin, and skeletal muscle to whole-body protein synthesis in the young lamb. Br J Nutr 1988; 60:77–84.
10. Raynes JG, Cooper EH. Comparison of serum amyloid A protein and C-reactive protein concentrations in cancer and non-malignant disease. J Clin Path 1983; 36:798–803.

11. Cooper EH, Stone J. Acute phase reactant proteins in cancer. *In* Klein G, Weinhouse S, ed. Advances in Cancer Research. New York: Academic Press, 1979, pp 1–44.
12. Heymsfield SB, McManus CB. Tissue components of weight loss in cancer patients: a new method of study and preliminary observations. Cancer 1985; 55:238–249.
13. Preston T, Fearon KCH, Robertson I, et al. Tissue loss during severe wasting in lung cancer patients. *In* Ellis KJ, Yasumura S, Morgan WD, eds. Vivo Body Composition Studies. London: Institute of Physical Sciences in Medicine, 1987, pp 60–69.
14. Kern KA, Norton JA. Cancer cachexia. JPEN 1988; 12:286–298.
15. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (peritoxins) and serum amyloid A protein. Advances in Immunology 1983; 34:141–212.
16. Gauldie J, Saunder DN, McAdam KPWJ, Dinarello CA. Purified interleukin-1 from human monocytes stimulates acute phase protein synthesis by rodent hepatocytes *in vitro*. Immunology 1987; 60:203–207.
17. Baumann H, Oncrato V, Gauldie J, Jahreis GP. Distinct sets of acute phase plasma proteins are stimulated by separate human hepatocyte-stimulating factors and monokines in rat hepatoma cells. J Biol Chem 1987; 262:9756–9768.
18. Gauldie J, Richards C, Harnish D, et al. Interferon $b_2$/B-cell stimulatory factor type 2 share identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute-phase protein response in liver cells. Proc Nat Acad Sci USA 1987; 84: 7251–7255.
19. Selby P, Hobbs S, Viner C, et al. Tumor necrosis factor in man: clinical and biological observations. Br J Can 1987; 56:803–808.
20. Geiger T, Andus T, Klapproth J, et al. Induction of rat acute phase proteins by interleukin 6 in vivo. Eur J Immunol 1988; 18:717–721.
21. Fleck A, Munro HN. The determination of organic nitrogen in biological material. Clin Chim Acta 1965; 11:2–12.
22. Read WWC, Harrison PA, Halliday D. A resin based method for the preparation of molecular nitrogen for $^{15}$N analysis from urinary and plasma components. Analyt Biochem 1982; 123:249–254.
23. Preston T, McMillan DC. Rapid sample throughput for biomedical stable isotope tracer studies. Biomedical and Environmental Mass Spectrometry 1988; 16:229–235.
24. Cannon JG, Van der Meer JWM, Kwiatkowsi D, et al. Interleukin IB in human plasma: optimization of blood collection, plasma extraction, and radio-immuno assay methods. Lymphokine Res 1988; 7:457–467.
25. Coulie PG, Cayphas S, Vink A, et al. Interleukin HP1 related hybroidoma and plasmacytoma growth factors induced by lipopolysaccharide in vivo. Euro J Immunol 1987; 17:1217–1220.
26. Picou D, Taylor-Roberts T. The measurements of total protein synthesis and catabolism and nitrogen turnover in infants in different nutritional states and receiving different amounts of dietary protein. Clin Sci 1969; 36:283–296.
27. Garlick PJ, McNurlan MA, Preedy VR. A rapid and convenient technique for measuring the rate of protein synthesis in tissues by injection of [$^3$H] phenylalanine. Biochem J 1980; 192:719–723.
28. Emery PW, Lovell L, Rennie JM. Protein synthesis measured in vivo in muscle and liver of cachectic tumour-bearing mice. Cancer Res 1984; 44:2779–2784.
29. Stein TP. Tumour-induced changes in the host's protein metabolism. *In* Arnott MS, Van Eys J, Wang YM, eds. Molecular Interrelations of Nutrition and Cancer. New York: Raven Press, 1982, pp 137–150.
30. Pain VM, Randall OP, Garlick PJ. Protein synthesis in lower and skeletal muscle of mice bearing an ascites tumor. Cancer Res 1984; 44:1054–1057.
31. Lundholm K, Edstrom S, Ekman L, et al. A comparative study of the influence of malignant tumor on host metabolism in mice and man. Cancer 1978; 42:453–461.
32. Emery PW, Edwards RHT, Rennie MJ, et al. Protein synthesis in muscle measured in vivo in cachectic patients with cancer. Br Med J 1984; 289:584–586.
33. Cryer DR, Matsushima T, Marsh J, et al. Direct measurement of apolipoprotein B synthesis in human very low density lipoprotein using stable isotopes and mass spectrometry. J Lipid Res 1986; 27:508–516.
34. Stovross MC, Fraker DL, Norton JA. Cachectin activity in the serum of cachectin, tumour-bearing rats. Arch Surg 1989; 24:94–99.
35. Jablons DM, McIntosh JK, Mule JJ, et al. Induction of Interferon-$B_2$/Interleukin-6 (Il-6) by cytokine administration and detection of circulating interleukin-6 in the tumour-bearing state. Ann NY Acad Sci 1989; 557:157–161.

# Intra-abdominal Abscess in Regional Enteritis

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**Intra-abdominal abscess (IAA) developed in 129 of 610 patients (21.2%) with Crohn's disease confined to the small bowel. The location of the abscess was intraperitoneal (IPA) in 109 (17.9%) and retroperitoneal (RPA) in 20 (3.3%). There was a marked preponderance of male patients in the retroperitoneal group (ratio, 18:2) ($p < 0.0001$). All 129 patients were operated on. Thirteen of one hundred nine patients (12%) with IPA were reoperated on for recurrent abscess, and nine (8.2%) for other reasons. External fistula developed in 24 patients (22%) after simple incision and drainage. Four (3.7%) died: one from hepatitis, and three from sepsis 5, 14, and 90 days after surgery. Of the 20 patients with RPA, two (10%) were reoperated on for recurrent abscess and four (20%) for other reasons. External fistula developed in two patients (10%). There were no deaths in this group. A small number of patients with IAA complicating regional enteritis had persistent sepsis causing postoperative death, which is, however, six times lower than in our comparable series of Crohn's (ileo)colitis.**

TRANSMURAL INFLAMMATION IS a well-recognized feature of regional enteritis.[1-3] Deep fissures frequently are present on histologic sections and are the basic pathologic feature responsible for perforating complications, such as fistula and abscess. Fistulous tracts that end blindly result in intra-abdominal abscess (IAA), which may be localized in the intraperitoneal or retroperitoneal tissues.[4]

The incidence of intraperitoneal abscess (IPA) in Crohn's disease ranges from 12% to 28% in reported series.[5-7] The overall incidence of retroperitoneal abscess (RPA) in Crohn's disease is considerably lower, ranging from 2.7% to 4.3%.[8,9] In this study we examine the records of all patients with intraperitoneal and retroperitoneal abscesses in regional enteritis. We also examined the records of 158 patients with regional enteritis operated on for intestinal obstruction for comparative purposes.

## Methods

The medical records of 610 patients with Crohn's disease limited to the small bowel admitted to The Mount Sinai Hospital between 1960 and 1984 were reviewed retrospectively. The diagnosis of Crohn's disease was based on criteria elaborated by Lockhart-Mummery and Morson,[10] Lindner, Marshak, et al.,[11] Korelitz et al.,[12] and Cook and Dixon.[13] The final selection of cases was made according to the standard criteria enumerated in another publication.[14]

Among the 610 patients with regional enteritis, there were 129 patients (21.2%) with IAA. The diagnosis of abscess was established by the finding of frank purulent fluid at laparotomy. Patients with perineal, perirectal, or superficial abscess of the abdominal wall were excluded unless they had concomitant IAA. Patients with IAAs that developed within 30 days of abdominal laparotomy also were excluded. We examined the records of 158 patients with regional enteritis operated on for intestinal obstruction to compare the disease durations. A stricture was defined as a fixed, localized narrowing of the small bowel detected by radiographic examination or surgery.

Data concerning the sex ratio of the patients were analyzed using the chi square test. The differences in means were assessed by the two-tailed (2p) t test for unpaired data.

## Results

Intra-abdominal abscesses developed in 129 of 610 patients (21.2%) with regional enteritis (Table 1). In 109 of

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TABLE 1. *Age, Sex, and Duration to Abscess Formation in 129 Patients with Intra-abdominal Abscess in Regional Enteritis*

| | IPA | RPA | Total | Patients Without Abscess |
|---|---|---|---|---|
| No. of Patients | 109 | 20 | 129 | 481 |
| Sex (Ratio: Male to Female) | 60:49 | 18:2$^{\#1}$ | 78:51 | 255:226 |
| Mean age at onset of Crohn's disease | 24.14 | 19.65 | 23.45$^{\#2}$ | 27.22$^{\#2}$ |
| Mean age at diagnosis of abscess | 31.96$^{\#3}$<br>(69–14) | 25.35$^{\#3}$<br>(49–15) | 30.94<br>(69–14) | — |
| Mean duration from onset of CD to abscess (yrs) | 7.7 | 5.7 | 7.4 | — |

Statistical significance, $^{\#1}p < 0.0001$; $^{\#2}p < 0.004$; $^{\#3}p < 0.04$.
CD, Crohn's disease.

these patients (17.9%), the abscess was intraperitoneal in location, and in 20 (3.3%) patients it was retroperitoneal. There was a very significant preponderance of male patients in the latter group (M:F ratio, 18:2) ($X^2 = 551$, DF = 1, $p < 0.0001$), which was not found in patients with IPA (M:F ratio, 60:49).

The mean age at the time of onset of Crohn's disease was lower for the 129 patients with abscess than for the control series of 481 patients (23.45 years *versus* 27.22 years, respectively; $p < 0.004$). The mean age at diagnosis of abscess was higher in patients with IPA when compared with those who developed RPA (31.96 years *versus* 25.35 years, respectively; $p < 0.04$). The mean duration of disease to development of abscess was 7.7 years (range, 0 to 36 years) in the intraperitoneal group compared with 5.7 years (range, 0 to 19 years) in the retroperitoneal group, but the difference was not statistically significant. However we found a significantly shorter mean duration of disease in patients with IAA compared with that encountered in the 158 patients with Crohn's disease of the small bowel operated on for obstructive indications (7.4 years *versus* 10.3 years, respectively; $p < 0.004$).

The sites of clinical presentation of the 129 abscesses are shown in Table 2, the vast majority occurring in the right lower quadrant of the abdomen.

Abdominal pain was the most common presenting symptom, occurring in 92 patients (84.4%) with IPA, and in all 20 patients with RPA. Pain referred along the genitofemoral, lumbar, or other retroperitoneal nerve was found in 13 patients (65%) with RPA. Diarrhea (50%), nausea and vomiting (30%), and anorexia (10%) were distributed equally in each group. Seventeen patients (15%) with IPA and four patients (20%) with RPA presented with gastrointestinal bleeding.

The most consistent physical finding was the presence of an intra-abdominal mass, occurring in 69 patients (63.3%) in the IPA group and in 15 patients (75%) with RPA. Signs attributable to irritation of the psoas muscle, a positive psoas sign, fixed flexion of the hip, or limitation of hip extension, were found in RPA only in 16 patients.

The mean temperature on admission was 100.7 F (range, 98 to 105 F) for patients with IPA and 100.6 F (range, 97.8 to 104.5 F) among those with RPA. The average leukocyte count was 11,500 (range, 4500 to 25,000) in the intraperitoneal group and 11,450 (range, 3900 to 19,000) in the retroperitoneal group. The average weight loss was 7.6 pounds (range, 0 to 43 pounds) in the intraperitoneal group, and 13.6 pounds (range, 0 to 55 pounds) in the retroperitoneal group.

Fifty-one patients (46.8%) who developed IPA and 11 patients (55%) who had RPA presented with an associated abdominal fistula. The incidence of extraintestinal manifestations (20%), free perforation (10%), and perianal disease (15%) was the same in both groups. No patient in this series developed small bowel cancer.

In the intraperitoneal group, 9 patients (8.3%) presented with their abscesses extending into the abdominal wall and 11 patients (10%) had pelvic abscesses. Of the pelvic abscesses, 4 (36.4%) were associated with ileovesical fistula.

The 109 patients with IPA consisted of 61 patients (56%) with spontaneous abscess and 48 patients (44%) with postoperative abscess. The 20 patients belonging to the retroperitoneal group consisted of 12 patients (60%) with spontaneous abscess and 8 patients (40%) with postoperative abscess. Previous operations for patients with postoperative abscess are shown in Figure 1. The proportion of patients developing postoperative IAA at various intervals following previous surgery is shown in Figure 2.

Nine patients (8.3%) with IPA and two patients (10%) with RPA had blood transfusions during their hospitalizations.

All patients with IAA were operated on, and the mean follow-up time after operation was 3.15 years (range, 0 to 23 years) (Fig. 3). In the 109 patients with IPA, 53 (48.6%) underwent a primary *en bloc* resection and 56 (51.4%) underwent other surgical procedures. Recurrent abscess occurred in 13 of these patients (12%) with IPA: seven patients had undergone primary resection, four patients had incision and drainage, and two patients had diverting ileostomy. The mean duration to reoperation was 6.48 years (range, 0.08 to 24 years). Nine patients (8.3%) were reoperated on for recurrent Crohn's disease at a mean

TABLE 2. *Sites of Clinical Presentation of 129 Intra-abdominal Abscesses in Regional Enteritis*

| Site | Intraperitoneal Abscess | Retroperitoneal Abscess |
|---|---|---|
| Right lower quadrant | 91 (83.5%) | 16 (80%) |
| Left lower quadrant | 6 (5.5) | 4 (20%) |
| Pelvic | 9 (8.3%) | 0 |
| Periumbilical | 3 (2.7%) | 0 |

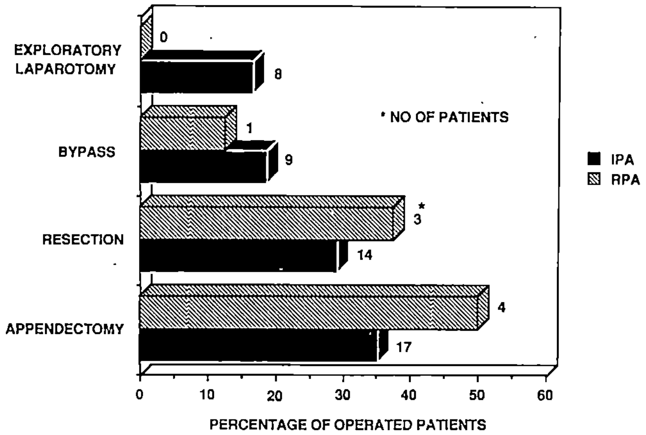

FIG. 1. Previous operation in 56 patients with postoperative abscess due to recurrent disease in regional enteritis.

duration of 3.5 years (range, 0.08 to 17 years). There were two recurrent abscesses (10%) among patients with RPA: one following resection and one after bypass.

There were four deaths in the series, two early and two late, all occurring in the IPA group, The one early death occurred in a patient with known Crohn's disease who also had abdominal Hodgkin's disease and presented with abdominal abscess. He underwent incision and drainage of the abscess and died 14 days after operation from gastrointestinal bleeding and sepsis. The second early death occurred in a patient with multiple abdominal abscesses. He underwent diverting ileostomy and died of sepsis 5 days after operation. Of the late deaths with IPA, one patient presented with free perforation and underwent incision and drainage of multiple abdominal abscesses. She did well after surgery and was discharged in 2 weeks. She returned 2 months later with fulminant hepatitis and died within 3 days. The other patient underwent ileocolic resection and never recovered from surgery. She remained septic and died 3 months later of pulmonary embolism. The surgical treatment and final outcome of the 129 patients are shown in Figure 3.

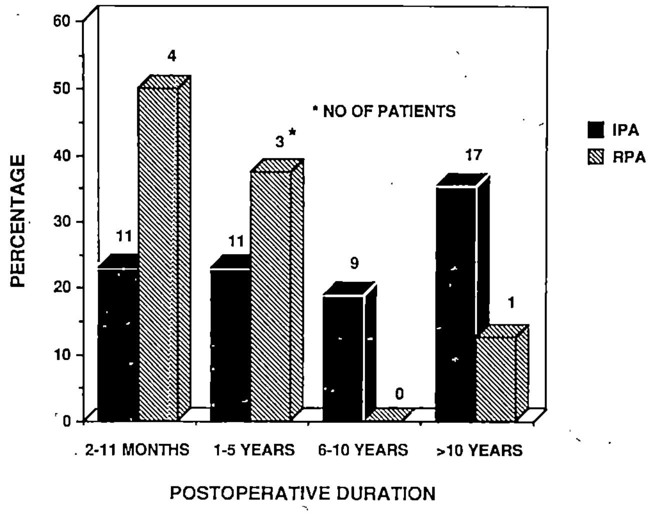

FIG. 2. Proportion of abscess at various intervals after previous surgery. Seventeen of forty-eight patients of the intraperitoneal group developed their abscess more than 10 years after previous operation.

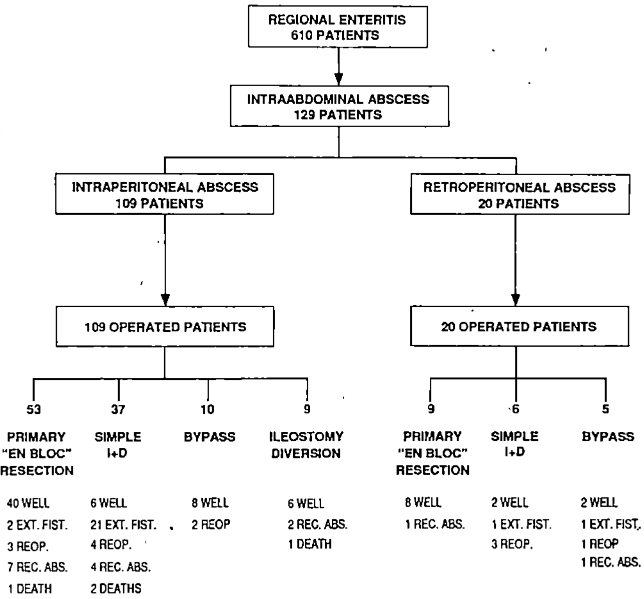

FIG. 3. Results of surgical treatment of abdominal abscess in 129 patients with regional enteritis.

## Discussion

In our series of 610 patients with Crohn's disease of the small bowel, IPA developed in 109 patients (17.9%) and RPA developed in 20 patients (3.3%). The 17.9% rate represents an incidence similar to the 20% rate (46 of 230 patients) previously reported by us for IAA in Crohn's disease involving the colon (16% for granulomatous colitis and 23% for ileocolitis)[15] and also is similar to that reported for IAA in Crohn's disease in the medical literature.[5-8,16]

There was no significant difference in the sex distribution for IPA, but in patients with RPA there was an overwhelming preponderance of male patients (18 of 20), for which there is no precedent in the Crohn's disease literature.[8,9,17,18] However our series is limited to regional enteritis and there is no other report of a large series with this combination.

It has been suggested that there are two forms of Crohn's disease: an inherently 'aggressive' form, and an 'indolent' form.[19,20] The amount of fibrosis may be a factor in differentiating these two forms of disease, with the 'aggressive perforating' type having less fibrosis.[21] Because fibrosis is a feature of cicatrizing Crohn's disease of long duration, it would be more prominent in obstructing disease. On the other hand, deep ulceration and fissure formation occurring earlier in the course of the disease with minimal fibrosis would result in abscess and fistula formation, and hence, earlier operation. We encountered a shorter duration of disease for patients with abscess when compared with patients who were operated on for obstructive indications. This finding supports the above theory. In addition we found a younger onset age for patients with abscess when compared with those without. This is consistent with the findings of DeDombal et al.,[19] who found a younger onset age, with a higher rate of mortality for the more aggressive form of disease.

The most striking difference in clinical symptoms between patients with IPA and those with RPA was the presence of evidence of psoas irritation in 16 patients (80%) of the latter group. This included fixed flexion or resistance to extension of the hip and a positive psoas sign.

Among 11 patients with pelvic abscesses, 4 (36.4%) had an associated ileovesical fistula. This finding usually can be determined clinically because most of these patients present with fecaluria and pneumaturia. In our series all four patients presented with at least one of those symptoms. In a previous publication we noted that one half of the 38 patients with ileovesical fistula developed sepsis, presumably from a pelvic abscess.[22] The other patients developed fistulae directly from the intestine into the bladder. Death occurred only in those patients with associated abscess.

We found a preponderance of the spontaneous type of abscess for both IAAs (56%) and RPAs (60%). This differs from the findings of Steinberg et al.,[5] who found a 78% incidence of postoperative abscess and a 22% incidence for the spontaneous type. Our higher incidence of spontaneous abscess may reflect a pattern of referral of complicated primary surgical cases to this hospital. The high proportion of postoperative abscesses reported by Steinberg et al.[5] may be due to a difference in anatomic distribution of disease because their series included patients with colonic disease. We agree with these authors that most late postoperative abscesses are the result of recurrent disease. However, among the postoperative abscesses, they found a 26% incidence of abscess within 1 month of surgery (12 of 46 abscesses) and only two (4%) more than 10 years after operation. By contrast, in our 48 patients with postoperative IPA, a high proportion of abscesses occurred in patients who had had their surgery more than 10 years earlier (17 patients, 35.4%). The single patient who developed his abscess within 30 days of surgery was excluded from the series because this represents a postoperative surgical complication rather than abscess due to recurrent or residual Crohn's disease.

In past years psoas abscess almost exclusively was due to tuberculosis with involvement of the lumbar vertebrae. In recent years tuberculosis has been virtually eradicated in industrialized countries. However, in recent years, there has been a slowly increasing incidence of this disease in major cities as a complication of Acquired Immunodeficiency Syndrome. Nevertheless the etiology of psoas abscess in these countries is now nonspecific intestinal disease. As the incidence of Crohn's disease has increased during the past 25 years,[23,24] this disease has become an increasingly common cause of psoas abscess in well-developed countries.[8] The 3.3% incidence in our series seems to favor this finding. In fact, in a recent review of the literature, Ricci et al.[25] found Crohn's disease the most common cause of secondary psoas abscess worldwide.

Some authors recommend percutaneous drainage for IAA.[26] Although none of the patients in this series were treated by this technique, we have since treated a few patients by this method, with limited success. We prefer surgical incision and drainage. We believe the reason for its failure in some patients is the large amount of necrotic tissue, which requires evacuation with the purulent fluid and cannot be aspirated. Because the fistulous tract is not removed, recurrent abscess with sepsis eventually develops. On the other hand, after surgical incision and drainage, persistence of the tract usually is followed by development of an external fistula, without sepsis, as occurred in 21 of 37 patients (56.8%) with IPA in this series. Second-stage definitive resection then can be carried out in a relatively clean field. However, in a small proportion of cases, 6 of 37 (16%) patients with IPA and 2 of 6 patients (33.3%) with RPA, no further treatment was required for a mean of 2.08 years.

As shown in Figure 3, primary *en bloc* resection was carried out in 62 of 129 patients with IAA, 53 in the intraperitoneal group, and 9 in the retroperitoneal group. A two-stage procedure (incision and drainage with later resection) was carried out in patients with enteroparietal abscess or patients who were seriously ill. Two patients died after incision and drainage before advancing to the second stage. One patient had complicated Crohn's disease, with multiple abscesses, and the other had abdominal Hodgkin's disease. No patients with incision and drainage for uncomplicated solitary abdominal abscess died.

In our previous publication[16] on IPA complicating Crohn's disease of the colon, 5 of 46 patients (11%) died within 32 days of the surgical procedure. By contrast only 2 of the 109 patients (1.8%) with small bowel disease in the present study died in the early postoperative period. In the former study, bypass or ileostomy diversion had the worst prognosis, with 4 deaths among 11 patients (36%). On the other hand, only 1 of the 19 patients treated by this method in this series (5.3%) died. This discrepancy in mortality rate between patients with IPA in regional enteritis and those with IPA secondary to colonic Crohn's disease might be explained by the difference in the intestinal bacterial flora, with the colon having a higher proportion of anaerobic bacteria.

Intra-abdominal abscess remains a serious complication of regional enteritis and causes very few deaths. For enteroparietal abscess, or patients who are seriously ill, incision and drainage with later definitive resection is the optimal therapy. In this study, however, primary *en bloc* resection was possible in 48% of all patients with IAA, with excellent results. On the basis of these results, we recommend primary resection as the treatment of choice for patients with uncomplicated IAA occurring in regional enteritis.

## Acknowledgment

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## References

1. Hadfield G. The primary histological lesion of regional enteritis. Lancet 1939; ii:773–775.
2. Morson BC. Histopathology of Crohn's disease. Proc R Soc Med 1968; 61:79–81.
3. Morson BC. The early histological lesion of Crohn's disease. Proc R Soc Med 1972; 65:71–72.
4. Greenstein AJ, Dreiling DA, Aufses AH, Jr. Crohn's disease of the colon. V. Retroperitoneal lumbocrural abscess in Crohn's disease involving the colon. Am J Gastroenterol 1975; 64:306–318.
5. Steinberg DM, Cooke WT, Alexander-Williams J. Abscess and fistulae in Crohn's disease. Gut 1973; 14:865.
6. Edwards H. Crohn's disease, an inquiry into its nature and consequences. Ann R Coll Surg Eng 1969; 44:121
7. Greenstein AJ, Kark AE, Dreiling DA. Crohn's disease of the colon. Am J Gastroenterol 1974; 62:419.
8. Kyle J. Psoas abscess in Crohn's disease. Gastroenterology 1971; 61:149–155.
9. Van Dongen LM, Lubbers EJC. Psoas abscess in Crohn's disease. Br J Surg 1982; 69:589–590.
10. Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis of the large intestine and distinction from ulcerative colitis). Gut 1960; 1:87–105.
11. Lindner AE, Marshak RH, Wolf BS, Janowitz HD. Granulomatous colitis: a clinical study. N Eng J Med 1963; 269:379–385.
12. Korelitz BI, Present DH, Alpert LI, et al. Recurrent regional ileitis after ileostomy and colectomy for granulomatous colitis. N Eng J Med 1972; 287:110–115.
13. Cook MG, Dixon MF. An analysis of reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis. Gut 1973; 14:255–262.
14. Greenstein AJ, Geller SA, Dreiling DA, Aufses AH Jr. Crohn's disease of the colon. IV. Clinical features of Crohn's (ileo) colitis. Am J Gastroenterol 1975; 64:191–199.
15. Greenstein AJ, Sachar DB, Greenstein RJ, et al. Intraabdominal abscess in Crohn's (ileo) colitis. Am J Gastroenterol 1982; 143: 727–730.
16. Nagler SM, Poticha SM. Intraabdominal abscess in regional enteritis. Am J Surg 1979; 137:350–354.
17. Burul CJ, Ritchie JK, Hawley PR, Todd IP. Psoas abscess: a complication of Crohn's disease. Br J Surg 1980; 67:355–356.
18. Ricci MA, Meyer KK. Psoas abscess complicating Crohn's disease. Am J Gastroenterol 1985; 80:970–977.
19. DeDombal FT, Burton I, Goligher JC. Recurrence of Crohn's disease after primary excisional surgery. Gut 1971; 12:519–527.
20. Sachar DB, Wolfson DM, Greenstein AJ, et al. Risk factors for postoperative recurrence in Crohn's disease. Gastroenterology 1983; 85:917–921.
21. Greenstein AJ, Lachman P, Sachar DB, et al. Perforating and nonperforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. Gut 1988; 29:588–592.
22. Greenstein AJ, Sachar DB, Tzakis A, et al. Course of enterovesical fistulas in Crohn's disease. Am J Surg 1984; 147:788–792.
23. Gilat T. The incidence of inflammatory bowel disease: going up or down? Gastroenterology 1983; 85:196–203.
24. Nunes GC, Ahlquist RE. Increasing incidence of Crohn's disease. Am J Surg 1983; 145:578–581.
25. Ricci MA, Rose FB, Meyer KK. Pyogenic psoas abscess: worldwide variation in etiology. World J Surg 1986; 10:834–843.
26. Gerzof SG, Robbins AH, Birkett DH, et al. Percutaneous catheter drainage of abdominal abscess guided by ultrasound and computed tomography. Am J Roentgenol 1979; 133:1–8.

# Risks of Intestinal Anastomoses in Crohn's Disease

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**Six hundred fifty-eight intestinal anastomoses in 429 operations for Crohn's disease were studied prospectively during an 8-year period to detect variables connected with perioperative morbidity. Postoperative complications occurred in 9.7% of the patients, 4% had to be reoperated on, and the overall mortality rate was 0.5%. In multivariate analysis by stepwise logistic regression, the only variable significantly ($p = 0.03$) associated with overall rate of complications was long-term corticosteroid therapy. Serious complications were more common in cases of intra-abdominal abscesses ($p = 0.01$) and preoperative steroid medication ($p = 0.03$). The combination of both of these risk factors increased the rate of reoperations from 0.6% (no steroids, no abscess) to 16% (steroids and abscess). No significant association with postoperative complications could be found for age, sex, duration of disease, previous operations, nutritional status, emergency surgery, extent of disease, type, number, and localization of anastomoses, presence of proximal ileo-/colostomy, or histologically inflamed margins of resection.**

SPECIFIC COMPLICATIONS OF intestinal anastomoses are predominantly septic ones being connected with intraoperative bacterial contamination.[1-3] Mechanical bowel preparation[4] and perioperative systemic antibiotic prophylaxis[3] may reduce the risk of anastomoses considerably. The rate of occurrence of the most severe common complication, *i.e.*, anastomotic leakage with consecutive peritonitis, depends, to a great deal, on surgical skills.[5] Wound infection rates of 0.3% and anastomotic leakage of 1.4% are reported for elective colonic resections in noninflammatory diseases.[6]

In Crohn's disease intestinal resections frequently are connected with factors known or suspected to increase the risk of complications. These are intestinal obstruction,[7] pre-existing septic complications,[8-10] impaired nutritional status,[11] chronic corticosteroid medication,[12] and need of multiple anastomoses. In addition inflammatory mediators such as prostaglandins with detrimental effects on anastomotic healing[13] may be synthesized more readily in Crohn's disease—even in uninflamed segments.[14] However patients undergoing operations for Crohn's disease usually are younger than patients undergoing resections for malignancy. Small bowel anastomoses often performed in Crohn's disease may bear a lower risk than colonic anastomoses.[15,16] Nevertheless postoperative complication rates reported in Crohn's disease tend to be higher than those seen in resection due to noninflammatory diseases: wound infections, 2% to 37%[2,3,17-19]; anastomotic leakage, 1.2% to 16.7%[2,17-20]; and death, up to 7%.[1,2,18-22] Lowest complication rates were reported by centers most experienced in the management of Crohn's disease.[17]

The present study intended to analyze complications of intestinal anastomoses in Crohn's disease in a large single-center experience.

## Materials and Methods

### *Patients*

During a period of almost 8 years (October 1981 to August 1989), 514 patients with Crohn's disease were admitted for surgical procedures to the Department of Surgery of the University of Heidelberg. All laparotomies with at least one intestinal anastomosis (partial or circumferential) were included in the present analysis, for a total of 429 operations (excluding reoperations for postoperative complications) during 424 admissions of 368 different individuals. Only cases with histologic proof of Crohn's disease were included.

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### Documentation

Throughout the period of study, all anamnestic, peri- and postoperative data used for this analysis were recorded prospectively.

### Definition of Complications

*Wound infection:* Any fluid drainage from a primarily closed abdominal incision was regarded as wound infection. Temporary redness of incision or inflammation of stitches subsiding after removal of stitches was not included. When pre-existing septic lesions such as enterocutaneous fistulas were left open for secondary healing, they were not counted as wound infections.

*Postoperative abdominal abscess:* No routine examinations were done after operations. In cases of unexplained fever or abdominal tenderness, ultrasound and/or computed tomographic scan were performed. Persisting localized fluid collections easily accessible with a needle were drained percutaneously, while others were drained by relaparotomy. With either purulent appearance or positive bacterial cultures, these fluid collections were considered abscesses.

*Anastomotic dehiscence:* No attempt was made to detect subclinical anastomotic leakage by routine radiologic investigation. Immediate contrast studies and/or reoperations were performed in cases of suspicion on clinical grounds.

*Severe complication:* All possibly life-threatening complications and all complications requiring reoperations were classified as severe for statistical analysis.

*Other complications:* All other postoperative complications during hospital admission were included, except lower urinary tract infections and upper respiratory infections.

### Nutritional Support

All patients presenting with a serum albumin level less than 30 g/L underwent preoperative parenteral nutrition (except three with emergency procedures): 35 to 40 kcal/kg/day were administered as a mixture of amino acids, carbohydrates, and fat for a minimum of 5 days, usually for 8 to 10 days.

### Enteric Preparation

For all elective procedures with expected left-sided colonic anastomoses, 3 to 5 L of enteric lavage with electrolyte solutions (without antibiotics) were applied the day before surgery. In cases of planned small bowel resections or ileocolic anastomoses, no mechanical bowel preparation was done.

### Use of Antibiotics

All patients with preoperatively apparent or suspected septic complications (fistula, abscess, or perforation) were given broad-spectrum antibiotics (cefotaxime: 2 g every 8 hours; metronidazole: 0.5 g every 8 hours) starting from the day of admission until 7 days after operation. Patients in whom these complications were detected during operation received the same regimen for 7 days. All other patients with enterotomies were subjected to perioperative antibiotic prophylaxis with two doses of 2 g mefoxitine spaced 8 hours apart.

### Technical Principles

Resections were carried out at the border of macroscopically detectable disease and no attempt was made to achieve histologically disease-free margins. Since 1984 strictureplasty has been used for smaller ileal and jejunal skip lesions. All anastomoses were carried out in a single-layer, end-to-end fashion, with interrupted vertical mattress sutures using absorbable suture material (polyglactin or polyglycolic acid, 3-0 or 4-0). To avoid fistula formation, intra-abdominal drains were never used close to anastomoses and only rarely in cases of (usually extraperitoneal) abscess cavities. Whenever possible omentoplasty was performed in presence of fistulas or abscesses. Ileostomy was used either to deviate intestinal contents from severe perianal and enterogenital fistulous disease or in selected cases of colocolic and ileorectal anastomoses with concurrent intra-abdominal septic/fistulous complications.

### Histologic Margin

Mild unspecific inflammatory changes at the margins of resected specimens were not considered. However all cases with significant inflammation at margins were included as affected by disease, regardless of specifity.

### Statistical Analysis

Possible associations of variables with either severe postoperative complication or any complication at all (see above) were evaluated by univariate chi square test (with Yates' correction for 1 degree of freedom) following classification as shown in Table 3. In addition 12 variables were used for multivariate analysis by stepwise logistic regression based on the same categories.

## Results

Types of procedures performed and types of complications encountered are listed in Tables 1 and 2. Of a total of 658 intestinal anastomoses, 491 were fully circumferential; the remaining consisted of strictureplasties,

TABLE 1. *Type of Operative Procedures*

| Procedure | Number |
|---|---|
| Gastroenterostomy | 4 |
| Jejunal resection | 11 |
| Ileal resection | 83 |
| Strictureplasty | 70 |
| Ileocecal resection/right hemicolectomy | 212 |
| Resection of previous anastomosis | 51 |
| Colic resection | 99 |
| Proctectomy/proctocolectomy* | 3 |
| Closure of ileostomy/colostomy | 36 |
| Closure of enteric fistula† | 66 |
| Closure of vesical/genital fistula | 29 |
| Other | 28 |

Many patients had more than one procedure.

* Included in this series are only patients with concomitant intestinal anastomosis.

† Mainly secondary defects, not including resected interenteric fistulas.

simple closures of inter-enteric fistulas, and closures of loop ileostomies. Twenty-one operations were emergency procedures in cases of severe bleeding, free bowel perforation, toxic colon, or advanced intestinal obstruction; there was no increase in complications for this subgroup.

### *Patient Characteristics*

Mean age of patients in this series was 33.1 years (range, 14 to 80 years), with anamnestic duration of symptoms for 7.6 ± 5.8 years (mean ± STD). Assuming that very young and elderly patients or those with a short and dramatic course or very long-standing disease should be more prone to complications, these variables were classified as shown in Table 3. However there was no significant difference in complication rates. In addition analyzing these variables as unclassified data did not reveal any difference (Wilcoxon test). Neither sex (chi square test)—57.8% of patients were female—nor number of previous operations related to Crohn's disease (Table 3) had any influence on complications.

TABLE 2. *Postoperative Complications*

| Type of Complications | Overall/Severe |
|---|---|
| Abdominal Septic | |
| Wound infection | 16/0 (3.7%/—) |
| Abdominal abscess | 7/4 (1.7%/0.9%) |
| Anastomotic dehiscence | 9/9 (2.1%/2.1%) |
| Abdominal nonseptic | |
| Intestinal obstruction | 6/4 (1.4%/0.9%) |
| Hemorrhage | 2/1 (0.5%/0.2%) |
| Suspected peritonitis* | 1/1 (0.2%/0.2%) |
| Other | |
| Septic coxitis | 1/1 (0.2%/0.2%) |
| Central venous line infection | 2/0 (0.5%/—) |
| Urosepsis | 2/0 (0.5%/—) |
| Pneumonia | 4/2 (0.9%/0.5%) |
| Venous thrombosis | 1/0 (0.2%/—) |
| Psychiatric/neurologic | 2/0 (0.5%/—) |
| No complications | 383 (90.3%) |
| Death | 2 (0.5%) |

Some of the complications listed above occurred in the same patient.

* Not confirmed at laparatomy.

TABLE 3. *Categorized Variables and Frequencies*

| Variables | n | Postoperative Complications Any (%) | Postoperative Complications Severe (%) |
|---|---|---|---|
| Age (years) | | | |
| <20 | 29 | 10.3 | 0.0 |
| 20–50 | 359 | 9.5 | 4.2 |
| >50 | 36 | 11.1 | 5.6 |
| Duration of symptoms (years) | | | |
| <1 | 45 | 11.1 | 2.2 |
| 1–10 | 263 | 9.1 | 3.8 |
| >10 | 116 | 10.3 | 5.2 |
| Number of previous operations | | | |
| 0 | 185 | 8.7 | 4.9 |
| 1 | 127 | 10.2 | 3.9 |
| 2 or more | 112 | 10.7 | 2.7 |
| Serum albumin < 30 g/L on admission | | | |
| Yes | 87 | 11.5 | 3.5 |
| No | 337 | 9.2 | 4.2 |
| Corticosteroids | | | |
| None | 89 | 6.7 | 0.0 |
| Perioperative | 70 | 2.9 | 1.4 |
| Preoperative | 265 | 12.5 | 6.0 |
| Preoperative septic complications | | | |
| None | 223 | 8.1 | 3.1 |
| Internal fistula | 130 | 10.8 | 2.3 |
| Abscess | 65 | 12.3 | 10.8 |
| Perforation | 6 | 16.7 | 0.0 |
| 'Perforating' disease* | | | |
| Yes | 201 | 11.4 | 5.0 |
| No | 223 | 8.1 | 3.1 |
| Extent of disease | | | |
| Only small bowel | 165 | 7.3 | 2.4 |
| Only large bowel | 61 | 13.1 | 6.6 |
| Small + large bowel | 177 | 10.2 | 4.5 |
| Not detectable† | 21 | 14.3 | 4.8 |
| Ileo-/colostomy proximal of anastomosis | | | |
| Yes | 51 | 7.8 | 3.9 |
| No | 373 | 9.9 | 4.0 |
| Number of anastomoses | | | |
| 1 | 286 | 8.7 | 3.9 |
| 2 | 90 | 12.1 | 5.5 |
| 3 or more | 48 | 10.4 | 2.1 |
| Location of anastomosis‡ | | | |
| Small/small bowel§ | 93 | 9.7 | 4.3 |
| Ileocolic | 231 | 9.1 | 3.0 |
| Colocolic | 58 | 12.1 | 5.2 |
| Ileorectal | 42 | 9.5 | 7.1 |
| Inflammation at margin# | | | |
| None | 155 | 7.7 | 4.5 |
| One margin | 91 | 6.6 | 3.3 |
| Both margins | 71 | 11.3 | 5.6 |

* According to the definition of Greenstein et al.[23]

† Cases with closure of ileostomy and no detectable disease at time of surgery.

‡ In cases of multiple anastomoses analysis for nonanastomotic complications was based on the most distal anastomosis.

§ Including gastroenterostomies.

# In 107 cases no resected specimen was available or pathologic workup was incomplete.

### *Nutritional Status*

Low serum albumin on admission was not associated with increased perioperative morbidity (Table 3). All patients presenting with serum albumin levels less than 30 g/L received preoperative parenteral feeding, except three patients with emergency procedures. Hereby 57% of the patients in this subgroup responded with normalization of serum albumin. However neither serum albumin at time of surgery nor reduction in ideal body weight predicted postoperative complications.

### *Medication*

Patients on corticosteroids at the time of admission (62.5%) received increased perioperative doses with continuing medication on discharge. These patients were significantly more prone to postoperative complications (Table 3). Others were not on corticosteroids either due to preferences of their physician, side effects, refusal by the patients, or inactive disease (*e.g.*, for closure of ileostomy). Until 1985 these patients were maintained off steroids throughout, and thereafter those consenting patients received perioperative steroids as part of an ongoing observational study on recurrence after Crohn's disease surgery (50 to 100 mg prednisone during operation, 7.5 to 10 mg continuing for 3 months). This change in policy had no significant effect on immediate complications of this subgroup (Table 3).

### *Extent and Activity of Disease*

The extent of disease within the gastrointestinal tract had no detectable influence on complications, nor did the presence of internal fistulas (Table 3). Severe complications were increased significantly in patients with pre-existing abscesses. However classification into 'perforating and nonperforating' disease[23] could not predict complications (Table 3). In addition there was no correlation with the length of resected bowel.

### *Anastomosis*

No change in complication rates was observed in patients with diverting ileostomy or colostomy. The location of the anastomoses along the gastrointestinal tract did not relate to the incidence of complications. Histologically inflamed margins at the site of anastomosis did not increase the rate of complications. One hundred thirty-eight patients received more than one anastomosis during the same procedure (maximum, 9) without increased risk (Table 3). There were 9 cases of anastomotic dehiscence, including 1 ileoileal, 4 ileocolic, 3 colocolic (1 of these was noncircumferential closure of secondary defect of an interenteric fistulas), and 1 ileorectal anastomosis. Two of these patients had protective ileostomies primarily, all of them underwent relaparatomy, and two of them died due to complications of septicemia.

### *Multivariate Analysis*

Stepwise logistic regression analysis for all categories of the variables listed in Table 4 gave essentially the same results as univariate statistics. Using a cut-off limit of $p < 0.05$, the only variable predicting overall complications was preoperative corticosteroids. Serious complications were associated with preoperative steroids ($p = 0.03$) and pre-existing abscesses ($p = 0.01$). One hundred sixty-four patients with no preoperative steroids and no abscess experienced one serious complication (0.6%), 216 with steroids but no abscess had 9 complications (4.2%), and 44 with both had 7 (16%) serious complications.

### *Other Complications*

All four cases of pneumonia and one of coxitis occurred in connection with intra-abdominal septic complications. There were no cases of clinically evident pulmonary embolism or serious cardiovascular complications. No deaths occurred, except with anastomotic breakdown.

## Discussion

The fact that sex, age, and duration of symptoms have no influence on postoperative complications is well in accordance with previous studies.[1,11,17] An increased risk for patients older than 65 years[16] could not be verified.

### *Nutrition*

Whether biochemical and anthropometric nutritional variables do[11,17] or do not[1,24] identify patients at risk to develop postoperative complications remains controver-

TABLE 4. *Association with Postoperative Complications*

| Variable | DF | p values<br>Any | p values<br>Severe |
|---|---|---|---|
| Age | 2 | 0.94 | 0.48 |
| Duration of symptoms | 2 | 0.88 | 0.67 |
| Number of previous operations | 2 | 0.82 | 0.65 |
| Low serum albumin | 1 | 0.66 | 1.0 |
| Corticosteroids | 2 | 0.03 | 0.02 |
| Preoperative septic complications | 3 | 0.64 | 0.02 |
| 'Perforating' disease | 1 | 0.18 | 0.47 |
| Extent of disease | 3 | 0.48 | 0.52 |
| Protective Ostomy | 1 | 0.83 | 1.0 |
| Number of anastomoses | 2 | 0.61 | 0.59 |
| Location of anastomosis | 3 | 0.93 | 0.59 |
| Inflammation at margin | 2 | 0.57 | 0.77 |

Differences are calculated by chi square test; for explanation of categories see Results.

DF, degrees of freedom.

sial. Preoperative total parenteral nutrition can improve nutritional parameters and close enterocutaneous fistulas.[25] However it contributes considerably to the costs of treatment and no randomized study has proved its value. In the present series, malnutrition indicated by low serum albumin or decreased body weight was not associated with differences in complication rates. However a possible association may have been obscured by the routine administration of preoperative parenteral feeding for patients with low albumin. Further studies are required to differentiate between the two possibilities that either malnutrition is no risk factor and preoperative parenteral feeding is unnecessary or malnutrition is indeed a risk being reduced by parenteral nutrition. The latter possibility is not excluded by our observation that nonresponding patients (no normalization of serum albumin after 10 days of parenteral feeding) did as well as responding patients because an improvement in wound healing was reported[26] after just 1 week of intravenous nutrition even before nutritional parameters show any change. Recent calorie intake may be more important than nutritional status.[27]

### *Corticosteroids*

Whether corticosteroids at clinical dosage may impair healing of intestinal anastomoses remains unclear. Experimental data indicate that very high doses are needed to interrupt anastomotic healing.[12] Clinical studies in Crohn's disease were not able to demonstrate specific risks.[1,17,28] However these authors did not make a distinction between long-term preoperative and limited perioperative use. The increase in complications observed in the present study for long-term steroid medication may be just a reflection of disease activity and severity rather than specific drug side effects. However the amplification of the detrimental effect of steroids in presence of abscesses may indicate specific immunosuppressive features.

In large controlled trials, corticosteroids have been proved to be an effective medical therapy for active Crohn's disease while being inefficient in quiescent disease.[29,30] The effect of operation itself on disease activation remains undetermined. A systematic endoscopic evaluation following supposedly radical resection was able to detect early anastomotic recurrence in most patients.[31] Whether this is related to the natural history of the disease itself or to local inflammatory activation induced by healing processes at the anastomosis remains an open question. Concerned about the latter possibility, especially in cases of nonradical surgery, we decided in 1985 to advice all patients who were off steroids to take this drug for 3 months after operation. The present data indicate no negative effect of this strategy on immediate postoperative complications. Data on recurrence rates are not yet complete.

### *Extent and Severity of Disease*

In accordance with previous reports,[17] we were unable to detect increased rates of complications in patients with extensive disease. However the same authors found a correlation with length of resection, a fact not demonstrable in our data. In case of preoperative septic complications, postoperative morbidity of almost 50% has been reported.[32] Analyzing separately a subgroup of patients with either fistulas, abscesses, or free perforations ('perforating' disease) who are more likely to experience early disease recurrence,[23] we and others[17] could not verify a difference in perioperative risk. However the subgroup presenting with intra-abdominal abscesses is more prone to a difficult postoperative course.

### *Localization, Type, and Number of Anastomoses*

Multiple anastomses may be done without additional risks in Crohn's disease, just as in noninflammed bowel.[33] Colonic and small bowel anastomoses can be performed with the same degree of safety (see Lindhagen et al.[18,19] and present results). In addition even ileorectal anastomoses, which are reported[20,34] to bear higher risks, did as well as more proximal ones. Contrary to previous reports,[11,17] the presence or absence of diverting ostomies did not influence overall complications or leakage rates. This possibly reflects the fact that in the present series most diverting ileostomies were primarily performed to dry up severe pelvic fistulous disease rather than to protect anastomoses. However, looking at the subgroup of 42 ileorectal anastomoses, we found that all four complications occurred among those 24 without ileostomy. Thorough analysis did not disclose additional variables predicting the need for protective ileostomies in subtotal colectomies.

### *Limited Surgery*

Most of the patients with Crohn's disease will need surgery at some point during their lives.[35] Because surgery cannot be considered a curative measure,[31,36] the aim of operations has shifted from cure to management of complications while preserving as much intestine as possible.[37–39] Clinical recurrence does not occur more often if the margins of resection are histologically involved in the inflammatory process,[40,41] although this subject is still debatable for follow-up longer than 14 years.[42] Limited surgery, such as strictureplasties, neither predisposes to recurrence of stenosis at the very same site[43] nor leads to additional perioperative morbidity (no leakage in 70 strictureplasties in the present series). Secondary lesions of interenteric fistulas may be closed without resections, and protective ostomies recommended by some authors[22] for distal fistulas are not necessary. The present data support the strategy of limited surgery in Crohn's disease inasmuch as overall perioperative morbidity and mortality rates can be kept low; suturing microscopically inflamed bowel seems to be a safe procedure.

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## References

1. Allsop JR, Lee ECG. Factors which influenced postoperative complications in patients with ulcerative colitis or Crohn's disease of the colon on corticosteroids. Gut 1978; 19:729–734.
2. Barker K, Graham NG, Mason MC, et al. The relative significance of preoperative oral antibiotics, mechanical bowel preparation and preoperative peritoneal contamination in avoidance of sepsis after radical surgery for ulcerative colitis and Crohn's disease of the large bowel. Br J Surg 1971; 58:270–273.
3. Keighley MRB. Prevention and treatment of infection in colorectal surgery. World J Surg 1982; 6:312–320.
4. Crapp AR, Powis SJA, Tillotson P, et al. Preparation of the bowel by whole-gut irrigation. Lancet 1973; xx:1239–1240.
5. Fielding LP, Stewart-Brown S, Blesovsky L, Kearney G. Anastomotic integrity after operations for large-bowel cancer: a multicentre study. Br Med J 1980; 2:411–414.
6. Curley SA, Allison DC, Smith DE, Doberneck RC. Analysis of techniques and results in 347 consecutive colon anastomoses. Am J Surg 1988; 155:597–601.
7. Jönsson K, Jiborn H, Zederfeldt B. Healing of anastomoses after obstruction of small intestine. Surg Gynecol Obstet 1988; 167: 324–330.
8. Hesp FLEM, Hendriks T, Lubbers EJC, DeBoer HHM. Wound healing in the intestinal wall. Effects of infection on experimental ileal and colonic anastomoses. Dis Colon Rectum 1984; 27:462–467.
9. Greenhalgh DG, Gamelli RL. Is impaired wound healing caused by infection or nutritional depletion? Surgery 1987; 102:306–312.
10. Ballantyne GH. The experimental basis of intestinal suturing. Dis Colon Rectum 1984; 27:61–71.
11. Tartter PI, Driefuss RM, Malon AM, et al. Relationship of postoperative septic complications and blood transfusions in patients with Crohn's disease. Am J Surg 1988; 155:43–48.
12. Aszodi A, Ponsky JL. Effects of corticosteroids on the healing bowel anastomosis. Am Surg 1984; 50:546–548.
13. Brennan SS, Foster ME, Morgan A, Leaper DJ. Prostaglandins in colonic anastomotic healing. Dis Colon Rectum 1984; 27:723–725.
14. Post S, Betzler M, Goerig M, et al. Intestinal cyclooxygenase activity in Crohn's disease. Am J Gastroenterol 1987; 82:955.
15. Schofield PF, Manson JM. Indications for and results of operation in inflammatory bowel disease. J R Soc Med 1986; 79:593–595.
16. Tchirkow G, Lavery IC, Fazio VW. Crohn's disease in the elderly. Dis Colon Rectum 1983; 26:177–181.
17. Heimann TM, Greenstein AJ, Mechanic L, Aufses AH Jr. Early complications following surgical treatment for Crohn's disease. Ann Surg 1985; 201:494–498.
18. Lindhagen T, Ekelund G, Leandoer L, et al. Crohn's disease in a defined population. Course and results of surgical treatment. I. Small bowel disease. Acta Chir Scand 1983; 149:407–413.
19. Lindhagen T, Ekelund G, Leandoer L, et al. Crohn's disease in a defined population course and results of surgical treatment. Part II. Large bowel disease. Acta Chir Scand 1983; 149:415–421.
20. Cooper JC, Jones D, Williams NS. Outcome of colectomy and ileorectal anastomosis in Crohn's disease. Ann R Coll Surg Engl 1986; 68:279–282.
21. Valiulis A, Currie DJ. A surgical experience with Crohn's disease. Surg Gynecol Obstet 1987; 164:27–32.
22. Pettit SH, Irving MH. The operative management of fistulous Crohn's disease. Surg Gynecol Obstet 1988; 167:223–228.
23. Greenstein AJ, Lachman P, Sachar DB, et al. Perforating and nonperforating indications for repeated operations in Crohn's disease: evidence for two clinical forms. Gut 1988; 29:588–592.
24. Fasth S, Hulten L, Magnusson O, et al. Postoperative complications in colorectal surgery in relation to preoperative clinical and nutritional state and postoperative nutritional treatment. Int J Color Dis 1987; 2:87–92.
25. Gouma DJ, von-Meyenfeldt MF, Rouflart M, Soeters PB. Preoperative total parenteral nutrition (TPN) in severe Crohn's disease. Surgery 1988; 103:648–652.
26. Haydock DA, Hill GL. Improved wound healing response in surgical patients receiving intravenous nutrition. Br J Surg 1987; 74:320–323.
27. Windsor JA, Knight GS, Hill GL. Wound healing response in surgical patients: recent food intake is more important than nutritional status. Br J Surg 1988; 75:135–137.
28. Knudsen L, Christiansen L, Jarnum S. Early complications in patients previously treated with corticosteroids: a retrospective study of 250 operations on patients with Crohn's disease or ulcerative colitis. Scand J Gastroenterol 1976; 37(Suppl):123–128.
29. Malchow H, Ewe K, Brandes JW, et al. European cooperative Crohn's disease study (ECCDS): results of drug treatment. Gastroenterology 1984; 86:249–266.
30. Summers RW, Switz DM, Sessions JT Jr, et al. National cooperative Crohn's disease study: results of drug treatment. Gastroenterology 1979; 77:847–869.
31. Rutgeerts P, Geboes K, Vantrappen G, et al. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. Gut 1984; 25:665–672.
32. Hulten L. Surgical treatment of Crohn's disease of the small bowel or ileocecum. World J Surg 1988; 12:180–185.
33. Whelan RL, Wong WD, Goldberg SM, Rothenberger DA. Synchronous bowel anastomoses. Dis Colon Rectum 1989; 32:365–368.
34. Ambrose NS, Keighley MR, Alexander-Williams J, Allan RN. Clinical impact of colectomy and ileorectal anastomosis in the management of Crohn's disease. Gut 1984; 25:223–227.
35. Harper PH, Fazio VW, Lavery IC, et al. The long-term outcome in Crohn's disease. Dis Colon Rectum 1987; 30:174–179.
36. Greenstein AJ, Sachar DB, Pasternak BS, Janowitz HD. Reoperation and recurrence in Crohn's colitis and ileocolitis: crude and cumulative rates. N Engl J Med 1975; 293:685–690.
37. Herfarth C, Heil T. Morbus Crohn und Colitis ulcerosa—Standortbestimmung: Chirurgische Aspekte. Chirurg 1981; 52:749–757.
38. Lee ECG. Aim of surgical treatment of Crohn's disease. Gut 1984; 25:217–222.
39. Alexander-Williams J, Haynes IG. Conservative operations for Crohn's disease of the small bowel. World J Surg 1985; 9:945–951.
40. Chardavoyne R, Flint GW, Pollack S, Wise L. Factors effecting recurrence following resection for Crohn's disease. Dis Col Rectum 1986; 29:495–502.
41. Speranza V, Simi M, Leardi S, Del Papa M. Recurrence of Crohn's disease after resection. Are there any risk factors? J Clin Gastroenterol 1986; 8:640–646.
42. Krause U, Ejerblad S, Bergman L. Crohn's disease. A long-term study of the clinical course in 186 patients. Scand J Gastroenterol 1985; 20:516–524.
43. Alexander-Williams J, Haynes IG. Up-to-date management of small-bowel Crohn's disease. Adv Surg 1987; 20:245–264.

# A Clinical Pilot Study Combining Surgery with Intraoperative Pelvic Hyperthermochemotherapy to Prevent the Local Recurrence of Rectal Cancer

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**Intraoperative pelvic hyperthermochemotherapy (IOPHC) with mitomycin C (MMC) was prescribed for 14 patients with resectable advanced rectal cancer in an attempt to prevent a postoperative local recurrence. Immediately after rectal amputation and extended lymphadenectomy, IOPHC was performed using physiologic saline containing 40 μg/mL of MMC at 45.5 ± 0.6 C for 90 minutes, with an apparatus devised for IOPHC. At the end of IOPHC, the esophageal temperature was 37.2 ± 0.8 C and cooling was not required. Antitumor efficacy and complications in the IOPHC group were compared with findings in 12 rectal cancer patients who underwent surgery only within the same period of time. Operation time was not prolonged with IOPHC treatment. In cytologic examinations of the pelvic lavage just before IOPHC treatment, viable cancer cells were detected in 6 of the 14 patients but were never detected in the postoperative exudate drained from the pelvic cavity. Of the 12 patients in the control group, 2 had a local recurrence, while in the IOPHC group there was no local recurrence for 16.9 ± 9.7 months at this writing. Postoperative complications did not differ between the groups. This IOPHC treatment is a favorable method in eradicating cancer cells for postoperative local recurrence of rectal cancer.**

THE SURVIVAL OF patients with advanced rectal cancer has improved little despite advances in surgical techniques and postoperative care. About one half of the number of patients with a recurrent rectal cancer after curative surgery died of a local recurrence alone, without reliable evidence of any distant metastasis.[1-4] To improve the clinical outcome of rectal cancer patients, preoperative irradiation has been prescribed, with encouraging results.[5-8] Sugarbaker et al.[9] carried out a randomized trial of intraperitoneally administered 5-fluorouracil (5-FU) for 66 patients with advanced colorectal cancer. Although the incidence of postoperative hematogenous metastasis was much the same between the intraperitoneal and intravenous 5-FU groups, the former had a low incidence of intraperitoneal recurrence at p = 0.003, compared to the latter.

Hyperthermia has a selective cytocidal effect on cancer cells and enhances the antitumor effect of chemotherapeutic drugs. Whether hyperthermia can serve as an effective antitumor treatment depends on an apparatus capable of uniformly heating target tumors, at a tumorcidal temperature. In case of hyperthermic treatment for a deeply situated target tumor, it is most difficult to heat only the target tumor. Spratt et al.[10] reported that aggressive surgery for recurrent pancreatic tumors was performed with considerable success in combination with intraperitoneal hyperthermic chemotherapy. We prescribed intraperitoneal hyperthermic perfusion for patients with advanced gastric cancer and found that in cases of far-advanced gastric cancer, intraoperative peritoneal hyperthermic perfusion with mitomycin C (MMC) had a marked antitumor efficacy for cancer cells or cancer tissues in the abdominal cavity.[11,12] In gastric cancer patients with peritoneal seeding as well as large serosal invasion, survival rates of patients given the intraperitoneal hyperthermic perfusion exceeded those of patients treated with surgery only, with a statistical difference.[13] We devised an apparatus for heating the intrapelvic cavity and intraoperative hyperthermochemotherapy was given to patients with advanced rectal cancer to eradicate the residual cancer cells at the site of tumor invasion beyond the rectal wall. Clin-

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ical results of the intraoperative pelvic hyperthermochemotherapy (IOPHC) are described in this report.

## Patients and Methods

In October 1986 we initiated a hyperthermic study on rectal cancer, with physiologic saline at 45 to 47 C in the pelvic cavity, following the model of intraperitoneal hyperthermic perfusion for gastric cancer.[11,12] Clinical experience with hyperthermia for gastric cancer prompted us to develop a simply designed apparatus through which heat would be distributed uniformly throughout the pelvic cavity.

### *Intraoperative Pelvic Hyperthermochemotherapy*

Immediately after rectal amputation and extended lymphadenectomy, the pelvic cavity was filled with prewarmed physiologic saline containing 40 μg/mL of MMC (Kyowa Hakko Co. Ltd., Tokyo, Japan). The apparatus for intraoperative pelvic hyperthermochemotherapy (IOPHC) we designed (IOPHC-II type, Sakaguchi Electric Heater Co. Ltd., Tokyo, Japan) is submerged in the warmed saline and is connected to a heat and control system of IOPHC. When this apparatus is submerged in saline containing MMC, the saline can be warmed exactly at a monitored temperature (Fig. 1). The warmed saline circulates throughout the pelvic cavity. This treatment was given at 45.5 ± 0.6 C for 90 minutes. Throughout this IOPHC the temperature in the esophagus did not exceed 38.6 C in the 14 patients given IOPHC, with the mean esophageal temperature of 37.2 ± 0.8 C.

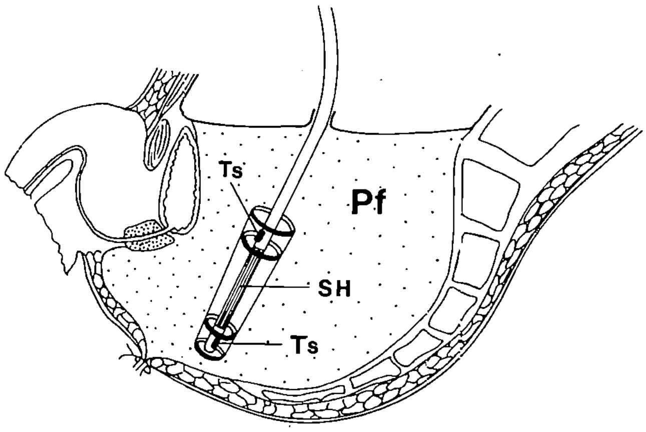


FIG. 1. Schema of the intraoperative pelvic hyperthermochemotherapy. Pf, perfusate; SH, sheathed heater; Ts, thermosensor.

TABLE 1. *Data on Patients*

| Data | IOPHC Group (n = 14) | Control Group (n = 12) |
|---|---|---|
| Age (years) | 61.4 ± 9.7 | 64.3 ± 10.8 |
| Sex (male/female) | 7/7 | 5/7 |
| Location of Primary Tumor | | |
| $R_s$ | 1 | 0 |
| $R_a$ | 0 | 1 |
| $R_{ab}$ | 3 | 1 |
| $R_b$ | 10 | 10 |
| Stage Grouping of TNM Classification | | |
| Stage I | 0 | 3 |
| Stage II | 2 | 4 |
| Stage III | 12 | 5 |
| Stage IV | 0 | 0 |
| Operation Undergone | | |
| Miles' method | 12 | 10 |
| Low-anterior resection | 2 | 2 |
| Operation time (hours) | 5.9 ± 1.1 | 5.3 ± 0.4 |

$R_a$, tumor located in upper rectum (above peritoneal reflection); $R_b$, tumor located in lower rectum (below peritoneal reflection); $R_{ab}$, tumor located in rectum at peritoneal reflection.

### *Patients and Treatments*

Fourteen patients with rectal cancer underwent rectal amputation followed by IOPHC (IOPHC group) and, within the same period of time, 12 patients with rectal cancer underwent surgery alone (control group). Clinicopathologic findings of these two groups are shown in Table 1. In 12 patients who were treated with Miles' operation in the IOPHC group, conventional colostomy was performed during the IOPHC treatment, and in two patients with low-anterior resection, an anastomosis was carried out after the IOPHC.

### *Laboratory Data and Cytologic Examinations*

During the IOPHC, blood and perfusate were sampled periodically. Mitomycin C levels in the blood and perfusate were measured by high-pressure liquid chromatographic (HPLC) assay with minimal assay levels of 2 ng/mL. Blood and liver function tests were performed before and after the IPHC.

Cytologic examinations were made during operation on pelvic lavage and after operation were performed on exudate drained from the pelvic cavity. The materials in the exudate were stained with Papanicolaou.

## Results

Background factors in both groups are shown in Table 1. The average age and male to female ratio did not differ between the groups. With respect to comparing the TNM stage, the IOPHC group was more advanced, compared with findings in the control group, with a significant difference at p = 0.0401. Operation time did not differ between the groups.

### *Mitomycin C Levels in the Perfusate and Circulating Blood*

Mitomycin C concentrations in the perfusate decreased by about 40% at 90 minutes after the onset of IOPHC and those in the peripheral blood did not exceed 0.1 μg/mL throughout the treatment (Fig. 2).

### *Antitumor Effects*

In 6 of the 14 patients given IOPHC, the pelvic lavage just after rectal amputation showed cytologically viable cancer cells, but there were no cancer cells in the postoperative exudate drained from the pelvic cavity (Fig. 3). Two of the twelve patients in the control group have a local recurrence of the cancer in the follow-up for 17.8 ± 8.3 months, whereas there was no recurrence in the IOPHC group for 16.9 ± 9.7 months.

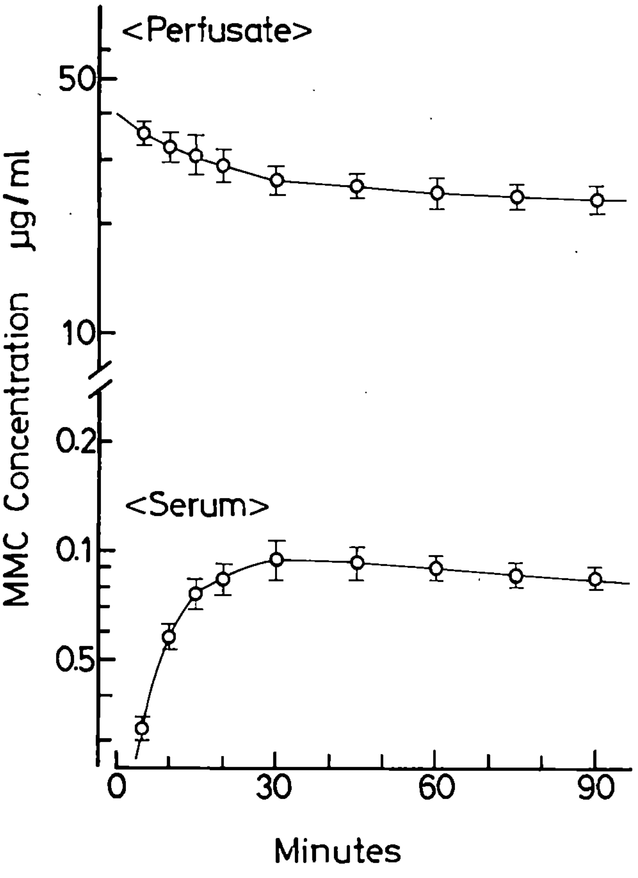
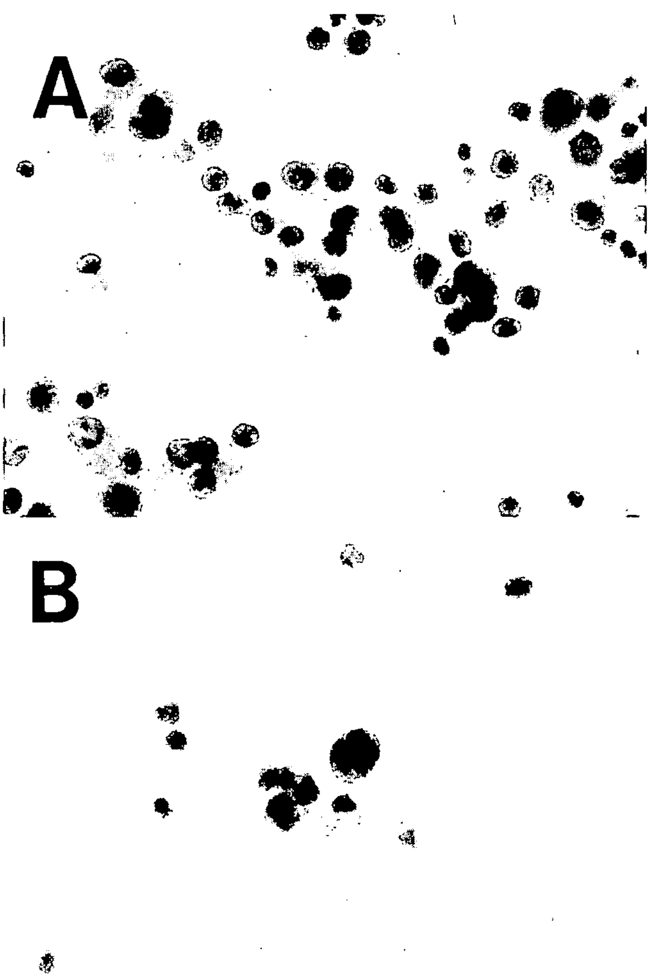


FIG. 2. Time course of MMC levels in the perfusate and peripheral blood. Each plot and vertical bar shows mean and SD, respectively.



FIGS. 3A and B. Cancer cells in the intraoperative pelvic lavage and in the postoperative exudate drained from the pelvic cavity (Papanicolaou, original magnification, ×120). (A) Before IOPHC. (B) Twenty-four hours after IOPHC.

### *Complications*

Postoperative complications are shown in Table 2. The incidence of the complications did not differ at p = 0.625 (chi square test = 2.533) between the groups. On the other

TABLE 2. *Postoperative Complications*

| Complication | IOPHC Group (n = 14) | Control Group (n = 12) |
|---|---|---|
| Ileus | 1 | 1 |
| Infection of pelvic cavity | 1 | 2 |
| Urinary retention | 3 | 2 |
| Fistula in the urinary bladder | 0 | 1 |
| Total amount of exudate drained from pelvic cavity (mL) | 1722 ± 1021 | 240 ± 123 |

hand, the total amount of postoperative exudate drained from the pelvic cavity was 1722 ± 1021 mL in the IOPHC group and 240 ± 123 mL in the control group, with a statistically significant difference at $p = 0.0000871$.

## Discussion

The intraoperative hyperthermochemotherapy we performed has proved to eradicate the rectal cancer cells left behind in the pelvic cavity during operation. A local recurrence develops from residual, microscopic cancer cells at operative margins in the vicinity of the gross tumor extension beyond the gut wall. The incidence of local recurrence following curative surgery alone is reported to be around 30% in patients with tumor extension beyond the rectal wall, without metastatic nodes, and to be about 50% in those with a similar local extent plus nodal involvement.[2-4,14,15]

Several reports on pre- and/or postoperative radiotherapies showed that local recurrence rates decreased and complications were minor.[5-8,15,16] Hoskins et al.[15] analyzed infield local recurrence in eight rectal cancer patients given postoperative irradiation and recommended that irradiation be started within 4 weeks after the surgery. They emphasized increasing the dose of radiation if the interval between surgery and radiation exceeds 6 weeks. This proposal is based on the premises of controlling and killing rectal cancer cells before the residual malignant cells survive and multiply in the pelvic cavity.

Cytologic findings of the pelvic lavage immediately after rectal amputation revealed viable cancer cells in 6 of the 14 patients; however, in the posthyperthermic exudate drained from the pelvic cavity, viable cancer cells were never present in those 14 patients. Accordingly this IOPHC treatment eradicated cancer cells spread and/or left behind in the pelvic cavity during surgical procedures.

In case of intraoperative peritoneal hyperthermic perfusion for gastric cancer, a considerable decrease was observed in the platelet count, serum protein and perfusate MMC levels. These events are caused by permeability of the peritoneum.[17] On the other hand, because the pelvic cavity does not have a peritonealized surface, the abovementioned side effects were not observed in case of IOPHC treatment. As shown in Figure 2, within 90 minutes after the onset of IOPHC, about 40% of MMC in the perfusate permeated *via* the pelvic wall, that is, 8 to 10 mg of MMC leaked into the peripheral blood within 90 minutes. This total amount of MMC is equivalent to one third to one fourth of the totally leaked MMC in case of the hyperthermic perfusion for gastric cancer. The minor side effects in this IOPHC treatment are due to the small amount of leaked MMC.

Higgins et al.[18] reported that a preoperative drug trial with floxuridine for rectal cancer did not decrease the percentage of nodal involvement, compared with surgery only. Agrez and Lieber[19] studied the drug sensitivity of 138 tumor samples taken from 135 colorectal cancer patients by means of a soft agar colony formation assay. They reported that the drug activity defined as 50% to 70% inhibition of colony formation was observed in 3 of 52 tumors with 10 μg/mL of 5-FU and in 4 of 52 with 0.4 μg/mL of MMC. These drug levels are equivalent to peripheral blood levels obtained by intravenous administration. Sugarbaker et al.[9] administered intraperitoneally 1360 mg of 5-FU in 2000 mL of fluid (680 μg/mL) and we administered intracavitarily 40 μg/mL of MMC. These levels are 70 to 100 times higher compared with the levels reported by Agrez and Lieber.[19] These high levels of 5-FU and MMC no doubt led to a favorable antitumor effect on colorectal cancer cells in the abdominal and pelvic cavities.

In all of the 14 patients given this IOPHC treatment, the postoperative exudate drained from the pelvic cavity increased significantly, compared to those in the control group. In case of the intraperitoneal hyperthermic perfusion for gastric cancer, a significant decrease in serum protein was observed along with the postoperative exudate drained from Douglas' pouch.[11,12] However, because the pelvic cavity has a small space and low permeability, compared with the abdominal cavity, a decrease in serum protein due to increased exudation is negligible.

Unlike intraperitoneal hyperthermic perfusion under hypothermia for gastric cancer, in case of IOPHC, the highest esophageal temperature did not exceed 38.6 C. Consequently all 14 patients tolerated this IOPHC treatment. Thus this IOPHC is a safe, reliable treatment to try to prevent local recurrence after rectal amputation.

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## References

1. Polk HC Jr, Spratt JS Jr. The results of treatment of perineal recurrence of cancer of the rectum. Cancer 1979; 43:952–955.
2. Malcolm AW, Perencevich NP, Olson RM, et al. Analysis of recurrence patterns following curative resection for carcinoma of the colon and rectum. Surg Gynecol Obstet 1981; 152:131–136.
3. Rich T, Gunderson LL, Lew R, Galdibini JJ, et al. Patterns of recurrence of rectal cancer after potentially curative surgery. Cancer 1983; 52:1317–1329.
4. Pilipshen SJ, Heilweil M, Quan SHQ, et al. Patterns of pelvic recurrence following definitive resections of rectal cancer. Cancer 1984; 53:1354–1362.
5. Roswit B, Higgins GA, Keehn RJ. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a National

Veterans Administration randomized study. Cancer 1975; 35: 1597–1602.

6. Higgins GA, Conn H, Jordan PH, et al. Preoperative radiotherapy for colorectal cancer. Ann Surg 1975; 181:624–631.
7. Stevens KR Jr, Allen CV, Fletcher WS. Preoperative radiotherapy for adenocarcinoma of the rectosigmoid. Cancer 1976; 37:2866–2874.
8. Mendenholl WM, Million RR, Bland KI, et al. Preoperative radiation therapy for clinically resectable adenocarcinoma of the rectum. Ann Surg 1985; 202:215–222.
9. Sugarbaker PH, Gianola FJ, Speyer JC, et al. Prospective, randomized trial of intravenous versus intraperitoneal 5-fluorouracil in patients with advanced primary colon or rectal cancer. Surgery 1985; 98: 414–422.
10. Spratt JS, Adcock RA, Muskovin M, et al. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980; 40:256–260.
11. Fujimoto S, Shrestha RD, Kokubun M, et al. Intraperitoneal hyperthermic perfusion combined with surgery effective for gastric cancer patients with peritoneal seeding. Ann Surg 1988; 208:36–41.
12. Fujimoto S, Shrestha RD, Kokubun M, et al. Clinical trial with surgery and intraperitoneal hyperthermic perfusion for peritoneal recurrence of gastrointestinal cancer. Cancer 1989; 64:154–160.
13. Fujimoto S, Shrestha RD, Kokubun M, et al. Positive results of combined therapy of surgery and intraperitoneal hyperthermic perfusion for far-advanced gastric cancer. Ann Surg 1990; 212: 592–596.
14. Mendenhall WM, Million RR, Pfaff WW. Patterns of recurrence in adenocarcinoma of the rectum and rectosigmoid treated with surgery alone: implication in treatment planning with adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1983; 9:977–985.
15. Hoskins RB, Gunderson LL, Dosoretz DE, et al. Adjuvant postoperative radiotherapy in carcinoma of the rectum and rectosigmoid. Cancer 1985; 55:61–71.
16. Gunderson LL, Dosoretz DE, Hedberg SE, et al. Low-dose pre-operative irradiation, surgery, and elective postoperative irradiation for resectable rectal and rectosigmoid carcinoma. Cancer 1983; 52:446–451.
17. Fujimoto S, Shrestha RD, Kokubun M, et al. Pharmacokinetic analysis of mitomycin C for intraperitoneal hyperthermic perfusion in patients with far-advanced or recurrent gastric cancer. Reg Cancer Treat 1990; 2:198–202.
18. Higgins GA, Humphrey EW, Dwight RW, et al. Preoperative radiation and surgery for cancer of the rectum. Veterans Administration Surgical Oncology Group trial II. Cancer 1986; 58:352–359.
19. Agrez MV, Lieber MM. In vitro chemotherapy sensitivity testing of primary human colorectal carcinomas. J Surg Oncol 1983; 22: 269–272.

# Liver Transplantation in Children

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**Although liver transplantation is now accepted as the ideal therapy for end-stage liver disease, relatively few centers have gained a large experience in children, and good results have been elusive. Technical difficulty and a high incidence of graft failure are among the obstacles to success. At the University of California at Los Angeles, 39% of our liver transplants are in the patients who are younger than 18 years. We have analyzed our experience with 103 patients to emphasize factors important to a favorable outcome with the procedure. One hundred twenty-three transplants were performed in 103 children (mean age, 5.2 years; 48% younger than 3 years). No reduced-size grafts were used. Scrupulous attention to technical details of the vascular reconstruction, including frequent use of the supraceliac aorta of the recipient and interrupted suture techniques, ensured construction of sound hepatic artery and portal vein anastomoses at the first operation. Preoperative exchange transfusions were used if the prothrombin time was prolonged beyond 7 seconds, resulting in an average blood loss of only 3.3 volumes. Cyclosporine dosage was maintained in the high therapeutic range for the first 4 weeks, and anti–T-cell antibody (OKT3) was used for rejection (38%). Amphotericin prophylaxis was used for biliary atresia patients with multiple previous operations. Eighty-two of one hundred three patients (80%) are alive. There were no intraoperative deaths. Actuarial survival rates at 6 months, 1 year, and 5 years are 80%, 79%, and 77%, respectively. Survival of patients who underwent transplantation at age less than 1 year is 65% *versus* 85% at age more than 1 year (p = 0.08). Retransplantation was performed in 19 patients (18%), with a survival rate of 58%. Hepatic artery thrombosis, the most frequent technical complication, occurred in only 16 patients (13%). Survival rates of ABO identical-match *versus* nonidentical-match grafts were 96% and 60%, respectively (p = 0.02). Graft survival was only 47% if more than one steroid cycle was needed, compared to 75% survival with OKT3 treatment. Despite impairment of renal function (glomerular filtration rate [GFR] less than 80 cc/kg/min) in 54% of patients and hypertension requiring therapy in 27%, 90% of the children demonstrated enhancement of growth, development, and functional status. The following conclusions were made. (1) Pediatric liver transplantation is the treatment of choice for all types of end-stage liver disease and should be considered early. (2) Factors that enhance survival include technical precision, aggressive retransplantation, antifungal chemoprophylaxis and therapy, and judicious immunosuppression with use of OKT3 for rejection. (3) A successful pediatric liver transplantation program will offer dramatic functional rehabilitation and long-term physical and intellectual growth and development for patients with an otherwise fatal disease process.**

ALTHOUGH CLINICAL LIVER transplantation was originally designed for and performed on children,[1] the experience with pediatric patients is far less than that which has accumulated for adults. Reasons for this are multifactoral and include shortage of small donors, lack of adequate experience in performing the procedures, and reluctance of some pediatricians and primary-care physicians to refer children with liver disease for transplantation.

Since the initiation of the the University of California at Los Angeles (UCLA) Liver Transplant Program in 1984, we have pursued actively the development and growth of a pediatric liver transplant unit. For nearly 5 years this represented the only major children's center in the West. At UCLA 39% of our liver transplants are performed in children younger than 18 years. We analyzed the cases of the first 103 transplant patients to emphasize factors important to a favorable outcome with the procedure.

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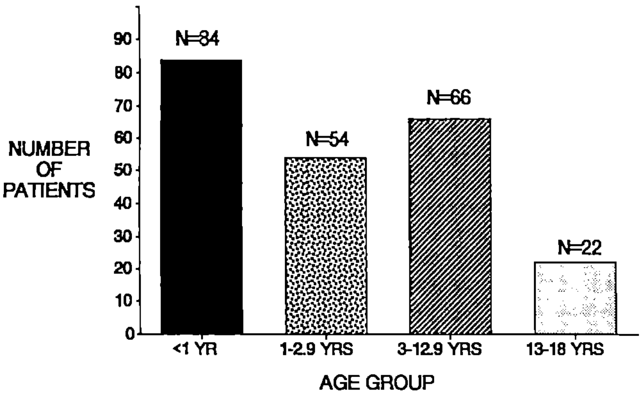


FIG. 1. Pediatric patients evaluated for OLT grouped by age.

## Methods

### *Evaluation*

Between January 1, 1984 and October 1, 1988, 225 children (135 female, 90 male) were evaluated for orthotopic liver transplantation (OLT). The age distribution is shown in Figure 1; of note 84 (37%) were 12 months old or younger. Of patients evaluated, 154 (68%) were accepted and placed on the active waiting list. Reasons for rejection were variable but most commonly reflected the extremes of pathology: either there was no clear indication for OLT or the patient was referred so late that multiple-organ failure developed. Diagnoses of patients evaluated and transplanted are shown in Figure 2.

The methods for evaluation and selection of children for liver transplantation have been described previously.[2] After evaluation patients are placed on the active waiting list if they suffer from end-stage liver disease resulting from any of the following conditions:

1. Biliary atresia with failure of a portoenterostomy.
2. Metabolic diseases associated with liver failure manifested by bleeding varices or abnormalities in hepatic synthetic function.
3. Cholestatic disorders that may not be an immediate threat to life but are responsible for an unacceptable lifestyle because of persistent jaundice, pruritus, fatigue, growth retardation, or inability to attend school.
4. Fulminant or subacute hepatic failure secondary to drugs, toxins, or hepatitis.
5. Primary liver tumors without extrahepatic spread.
6. Cirrhosis with a less predictable natural history but which is associated with bleeding varices uncontrollable by sclerotherapy or with impaired hepatocellular synthetic function.

Of the 154 children accepted for OLT, 123 transplants were performed on 103 patients. Mean age of the transplant recipients was 5.2 years. Figure 3 shows the overall age distribution. Ten per cent of patients on the active waiting list died before transplantation. This was due to lack of suitable donors in approximately one half of cases and to progression of disease in the others.

Attempts were made to match donors to recipients of identical blood types. Upper and lower limits of body-weight ratio, donor to recipient, were 2.5 and 0.5, respectively. No reduced-size grafts were used in this series.

### *Techniques*

The fundamental principles of donor retrieval, recipient hepatectomy, and liver grafting have been described extensively.[2–4] Several modifications of the procedure apply uniquely to children. The recipient hepatectomy in the patient with biliary atresia may be a formidable undertaking, particularly if the child has had several revisions of the portoenterostomy in attempts of salvage. In this setting, dense adhesions often bind the portal structures, duodenum, Roux-en-Y jejunal limb, and transverse colon

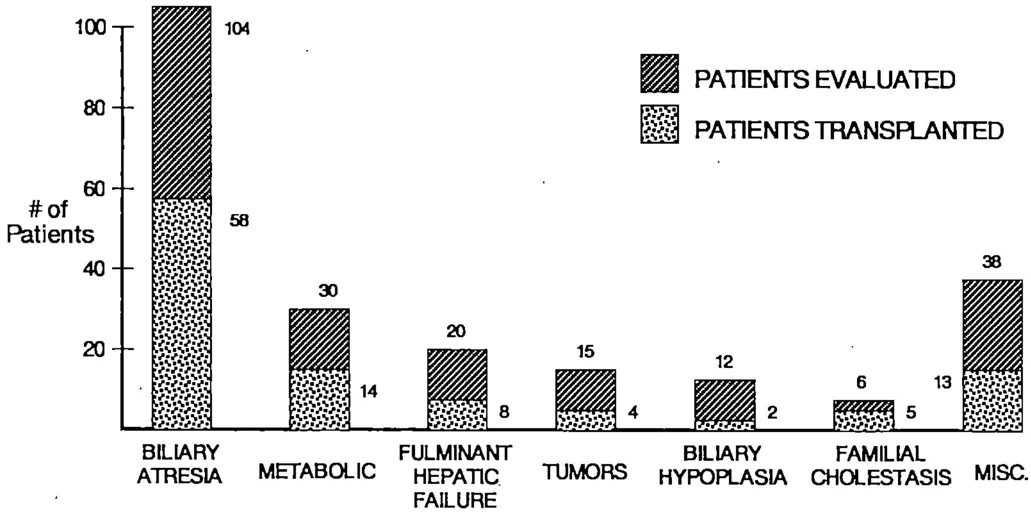


FIG. 2. Pediatric patients evaluated and number of transplants by diagnosis.

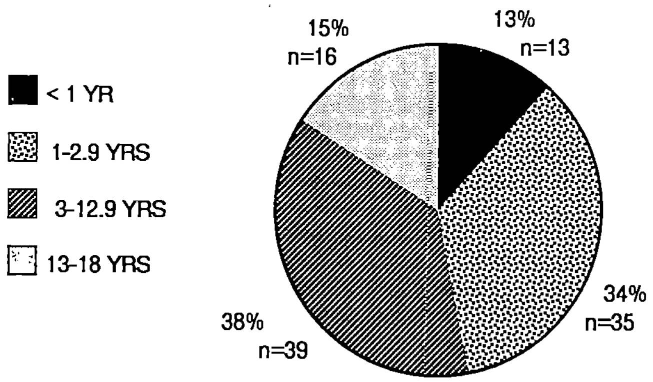


FIG. 3. Pediatric patients receiving OLT grouped by age.

into an unrecognizable and bloody tissue mass. To permit dissection without uncontrollable blood loss, unviolated tissue planes must be entered first. Thus dissection is begun with the posterolateral aspect of the right lobe of the liver, which usually is not scarred. In this plane, the transverse colon and second and third portions of the duodenum may be reflected down from the right lobe. Next the Roux-en-Y limb is identified at its point of entry through or above the transverse mesocolon and traced to the hilus of the liver. With the duodenum identified and separated, the limb is transected with a stapler and reflected inferiorly. This maneuver exposes the portal structures, which are easily identified lying below the divided limb. The conventional approach of hugging the undersurface of the liver to identify the components of the portal triad is bloodier and more prone to result in accidental enterotomies. Once the porta hepatis has been dissected, the portal vein is ligated very close to the liver, then divided to permit easy anterior access to the infrahepatic vena cava. Finally the suprahepatic vena cava is isolated.

The vascular anastomoses, particularly the hepatic artery, are most crucial for a satisfactory outcome. Important modifications that we have used to assure patency include (1) use of branch patch technique[4] to avoid intraluminal placement of sutures, (2) frequent use of the supraceliac aorta of the recipient as the arterial inflow vessel, (3) avoidance of the infrarenal aorta, which requires aortic conducts or long iliac artery grafts, and (4) use of intraoperative and postoperative low molecular-weight dextran (Rheomacrodex®, Pharmacia, Piscataway, NJ) followed by aspirin therapy. We have not found that an interrupted anastomosis is needed because we dissect back to an inflow vessel that is large enough for continuous suture. An exception is the portal vein anastomosis in infants smaller than 6 kg, in whom an interrupted 6-0 or 7-0 prolene suture technique is used. Biliary reconstruction is most commonly a 40-cm defunctionalized Roux-en-Y choledochojejunostomy. Duct-to-duct anastomoses are used infrequently in children.

### *Initial Immunosuppression*

Perioperative immunosuppression through May 1987 consisted of intravenous cyclosporine A (CsA) and methylprednisolone. The preoperative dose of CsA (15 mg/kg) was given orally. After operation, when urine output was established, the daily dose of CsA was 3 to 5 mg/kg given intravenously in two divided doses infused over 12 hours. An oral CsA dose (10 to 15 mg/kg/day given every 12 hours) was added when feeding resumed, and the IV dosage was tapered gradually. CsA trough plasma levels (Cyclosporine RIA-Kit, Sandoz, Basel, Switzerland) were determined daily, and the CsA dose was adjusted to maintain a therapeutic level between 200 and 300 ng/mL.

For the first five postoperative days, methylprednisolone was given in a rapidly decreasing dose, beginning at 20 to 30 mg/kg and tapering to 0.3 to 0.5 mg/kg. Maintenance oral prednisone later was substituted at this same dose.

In May 1987 initial immunosuppression with triple drug therapy was instituted. Intravenous azathioprine (1 to 2 mg/kg/day) administration was started on the first postoperative day and later converted to oral administration at the same dose. White blood cell count less than $4.0 \times 10^3$/mL, systemic sepsis, or pancreatitis were contraindications to starting azathioprine or continuing its use.

Between May 1987 and June 1988, patients were randomized into a trial using the monoclonal antibody OKT3 for rejection prophylaxis. Intravenous OKT3 was begun at 2.5 mg/day for children with body weights less than 30 kg or 5.0 mg for those greater than 30 kg. The first dose was given intraoperatively and then continued daily for 14 days. CD3+ cells in the peripheral blood were monitored, and the dose of OKT3 was increased if CD3 + percentage exceeded 10. During this trial methylprednisolone and azathioprine also were given as described above. CsA was begun on day 10 so that therapeutic levels would be achieved when OKT3 was stopped.

### *Maintenance Immunosuppression*

After discharge dual therapy with CsA and prednisone was used in our early experience then replaced by triple immunosuppression with the addition of azathioprine in May 1987. CsA levels were monitored regularly at each outpatient visit and the dose was adjusted accordingly, at intervals of once to twice per week for the first 2 to 4 weeks, biweekly for 1 to 2 months, and once every 3 to 4 weeks between 3 to 6 months after discharge. Thereafter, depending on the stability of the patient, CsA levels were measured at 2-month intervals. For the first year after OLT, trough plasma CsA levels were maintained at 200 to 250 ng/mL. After 1 year, in patients with stable liver function, the trough CsA levels were allowed to fall to a target of 140 to 160 ng/mL. Azathioprine was maintained at 1 mg/kg/day unless contraindications developed to preclude its use.

### *Treatment of Rejection*

Episodes of rejection suspected on clinical grounds were confirmed in most cases by percutaneous liver biopsy. Initial treatment consisted of intravenous methylprednisolone at 30 mg/kg/day, tapering over 5 days to the maintenance dose. In patients failing to respond to the steroid cycle, a second liver biopsy was obtained whenever possible. High-dose steroids were restarted, or a decision was made to treat with antithymocyte globulin (until June 1985) or OKT3 (thereafter). The dose of ATG was 50 mg given over 10 to 14 days. OKT3 was administered and monitored as outlined above.

### *Postoperative Management*

After OLT children were returned directly to the Pediatric Intensive Care Unit (PICU) under joint care of the pediatric intensivist, gastroenterologist, and transplant surgeon. Patients were monitored with cardioscope, central venous and arterial pressure lines, and pulse oximetry. Pulmonary artery catheters were used in patients with hemodynamic instability.

Initial ventilator setting include an $FiO_2$ of 1.0, tidal volume approximately 12 cc/kg, no positive end-expiratory pressure (PEEP), and a physiologic rate for age. Infants with body weights less than 8 kg were ventilated with pressure support at a pressure to give adequate chest excursion. The $FiO_2$ was weaned rapidly, and a PEEP of 3 to 4 cm $H_2O$ was added if the $FiO_2$ could not be decreased to 0.40 or less. Patients were extubated within 12 to 36 hours after operation, with supplementation by oxygen hood or mask, depending on age.

Vasoactive or inotropic agents initiated in the operating room were continued in the PICU. In addition low-dose dopamine (2 mcg/kg/min) was used in patients with previously diminished renal function and in those who developed renal dysfunction after operation. Hypertension was controlled with a combination of sublingual nifedipine and intravenous hydralazine.

Initial fluid management in the PICU was largely dependent on the patient's volume status on return from surgery, with hypernatremia and fluid overload a common pattern. Most patients receive $D_5W$ or $D_5$. 2NS with added potassium at limited volumes such that total fluid infusion was approximately 75% of calculated daily maintenance. Fresh frozen plasma was infused every 4 hours for 24 hours in patients transplanted through January 1987, but more recently was used only in patients with clinical bleeding. In the absence of significant bleeding, Dextran 40 was infused continuously for 7 days, then followed with daily low-dose aspirin. Hematocrit was maintained at 28% to 32%, with transfusion or phlebotomy and colloid replacement used as necessary. Coagulation studies were obtained daily. Hydrochloric acid (0.2 normal) is titrated to correct a base excess of 5 mmol/L (millimolar) or more, which occurs uniformly with a functioning graft.

All patients receive antibiotics for 48 to 72 hours after surgery. Ampicillin and cefotaxime was the standard regimen, with modifications made for pre-existing infections. If the donor had an infection, the recipient received a course of antibiotics appropriate for that infection. In addition all patients received oral nystatin and clotrimazole for fungal prophylaxis. Biliary atresia patients who had portoenterostomy revisions were treated prophylactically with low-dose amphotericin (0.3 mg/kg on alternate days) for 10 to 14 days.

Gastric pH was controlled with ranitidine and antacids. When total parenteral nutrition (TPN) was started on the first postoperative day, the ranitidine was given as a continuous infusion in the TPN.

## Results

### *Survival*

Of the 103 patients, 82 (80%) are alive to date. Survival of all patients according to age is shown in Figure 4. Survival for those younger than 1 year old was 65% *versus* 85% for those older than 1 year (p = 0.08). The overall 5-year actuarial survival rate is 77% (Fig. 5). Survival analysis among patients with biliary atresia, metabolic abnormalities, cirrhosis, and tumors shows the best prognosis for alpha-1-antitrypsin deficiency, with a 5-year survival rate of 95%. Patients with biliary atresia and tumors fared worse, with a 5-year survival rate of 71%.

Of the 21 deaths, four occurred within 10 days of transplantation as a result of brainstem herniation in patients with fulminant hepatic failure who never regained con-

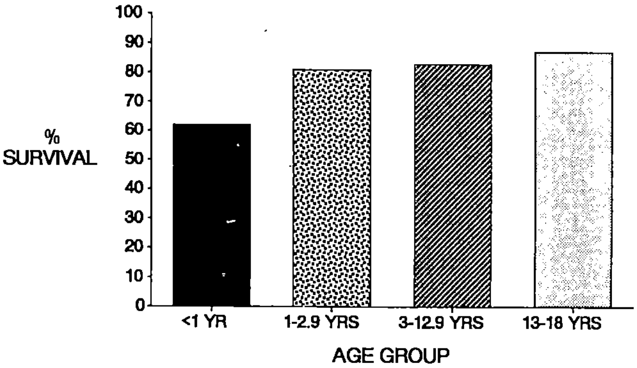


FIG. 4. Patient survival after OLT grouped by age.

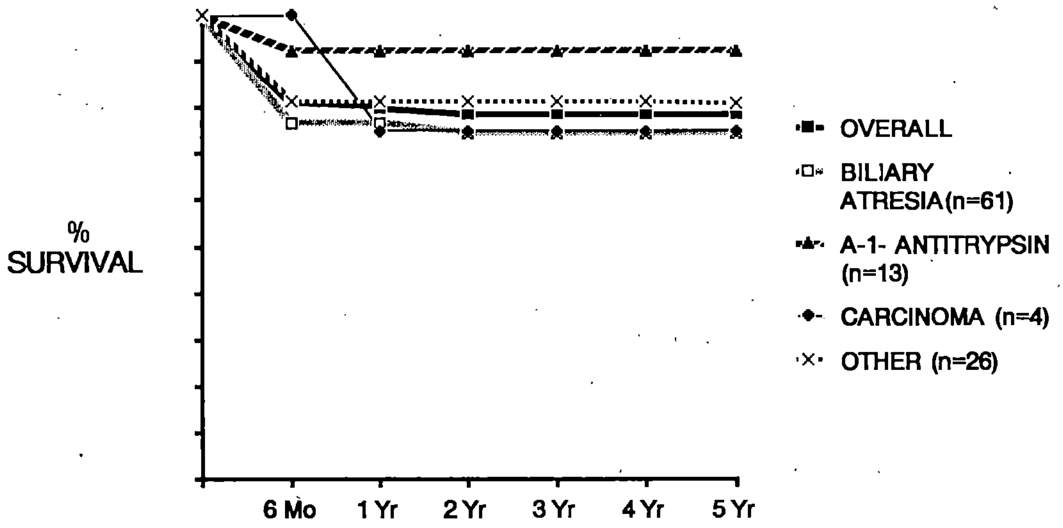


FIG. 5. Actuarial patient survival after OLT. Five-year overall survival of 77%. Kaplan–Meier method.

sciousness (two), bleeding and liver failure (one), and intrapulmonary bleeding (one). A detailed analysis of all causes of death is shown in Table 1.

There was a significant survival advantage when blood type matching was identical. In 82 transplants, an identical match was accomplished with a 96% survival rate. In con-

TABLE 1. *Death in 21 of 103 Patients*

| OLT# | Age | Disease | Cause of Death | Time After Transplantation | Comment |
|---|---|---|---|---|---|
| 10 | 4 yrs. | Biliary atresia | Bacterial sepsis | 2.5 yrs. | Normal LFT |
| 11 | 7 yrs. | Tyrosinemia w/hepatoma | Recurrent tumor | 10 mos. | Tumor involved hepatic |
| 16 | 8 mos. | Biliary atresia | Adenovirus infection | 17 days | Retransplanted for suspected rejection |
| 19 | 3 yrs. | Biliary atresia | Fungal sepsis | 7 weeks | |
| 23 | 12 yrs. | Biliary atresia | Fungal sepsis | 25 days | Extensive previous biliary surgery (12 operations) |
| 26 | 4 yrs. | Biliary atresia | Bacterial/fungal sepsis | 4.5 mos. | Retransplant H.A.T. |
| 31 | 2 yrs. | Fulminant hepatic failure | Brainstem herniation | 10 days | Did not regain consciousness |
| 48 | 14 mos. | Biliary atresia | Rejection | 1 yr. | Noncompliance |
| 51 | 14 yrs. | Alpha-1-antitrypsin | Ruptured splenic aneurysm | 5 days | Normal LFT |
| 75 | 10 mos. | Tyrosinemia | Intrapulmonary hemorrhage | 2 days | |
| 101 | 13 mos. | Biliary atresia | Sepsis | 12 days | Retransplant |
| 105 | 2 yrs. | Fulminant hepatic | Brainstem herniation | 3 days | Did not regain consciousness |
| 114 | 7 mos. | Biliary atresia | Respiratory failure | 22 days | |
| 123 | 2.5 yrs. | Biliary atresia | Sepsis/liver failure | 12 days | Retransplant for primary nonfunction |
| 134 | 11 yrs. | Cryptogenic cirrhosis w/ end-stage kidney disease | Sepsis | 2 mos. | Kidney transplant not performed |
| 143 | 11 yrs. | Gaucher's disease | Chronic rejection | 3 mos. | Intracerebral bleed, after OLT #1 retransplant for rejection |
| 161 | 8 yrs. | Familial cholestasis | Sepsis/intestinal infarction | 2 mos. | Retransplant H.A.T. |
| 163 | 5 mos. | Biliary atresia | Sepsis/respiratory insufficiency | 1 mos. | |
| 169 | 1 yrs. | Biliary atresia | Sepsis/liver failure | 1 mos. | Retransplant |
| 174 | 2 yrs. | Biliary atresia | HAT/sepsis | 18 days | Died awaiting retransplant |
| 216 | 2 yrs. | Biliary atresia | Sepsis/rejection | 14 days | Retransplant |

HAT, hepatic artery thrombosis.

trast, of 16 compatible but unidentical matches and five incompatible grafts, survival was 55% and 60%, respectively (Fig. 6).

### *Complications*

Technical complications most commonly appeared within 10 days of OLT. Hepatic arterial thrombosis (HAT) occurred most commonly and was seen in 16 of 123 cases (13%). Of these patients eight were younger than 2 years old; three required intraoperative revision of the anastomosis, and three received donor livers that required bench arterial reconstruction because of anomalies. None of these findings were significant ($p > 0.05$). The types of arterial reconstructions were variable and none had a significantly greater incidence of thrombosis. However use of the infrarenal recipient aorta for inflow with an aortic conduit or long iliac artery graft has been abandoned because of failure in two of four cases. Ten of sixteen patients with arterial thrombosis required retransplantation, six are currently alive without retransplant, and 13 of 16 are alive. Neither portal vein nor inferior vena cava (IVC) thrombosis was seen in this series. Two patients received superior mesenteric jump grafts for a thrombosed portal vein identified by pretransplant ultrasonography, and two patients with situs inversus had the donor infrahepatic vena cava oversewn because of a discontinuous IVC in the recipient.

Biliary tract complications were infrequent, occurring in only eight patients. The most common problem was a leak from the choledochojejunostomy in five (all requiring suture repair) and disruption in three requiring complete revision of the anastomosis. Late stenosis was seen in two patients who were treated with transhepatic balloon dilatation (Fig. 7). Intestinal perforation occurred in four patients with multiple revisions of the previous portoenterostomy. Of these three required diverting jejunostomy and one was repaired. Diagnosis was confirmed within 6 hours of perforation in all patients by the liberal use of a transtable lateral x-ray at first sign of abdominal distention (Fig. 8).

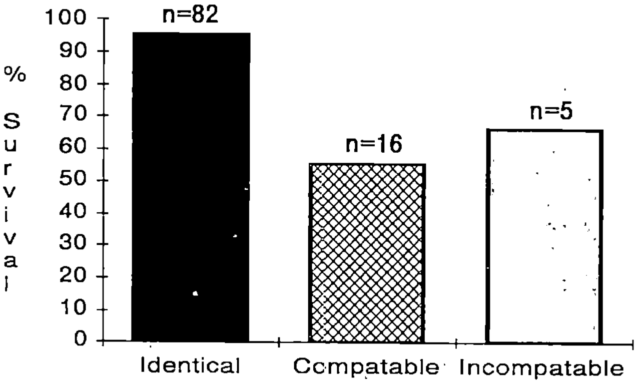


FIG. 6. First graft survival showing effects of ABO matching. Survival was 96%, 55%, and 60% for identical, compatible, and incompatible matches, respectively.

### *Renal Failure*

Renal function was studied in 48 patients treated with cyclosporine for more than 1 year. True GFR was measured by plasma clearance of Indium-111-DPTA. Seventy-three per cent of patients had true GFR less than 70 mL/min/1.73 $m^2$, while 85% had true GFR less than 90 mL/min/1.73 $m^2$, the lower limit of normal GFR in children (Fig. 9). The mean true GFR of patients treated with cyclosporine for more than 24 months was lower ($p = 0.02$) than for patients treated between 12 to 24 months. Pediatric OLT patients with normal true GFR (more than 90 mL/min/1.73 $m^2$) had significantly lower HPLC plasma cyclosporine levels. Fifty per cent of patients with a true GFR less than or equal to 50 mL/min/1.73 $m^2$ had hypertension. There was no effect on true GFR of age, liver function, azathioprine use, or peritransplant treatment with other nephrotoxic drugs.

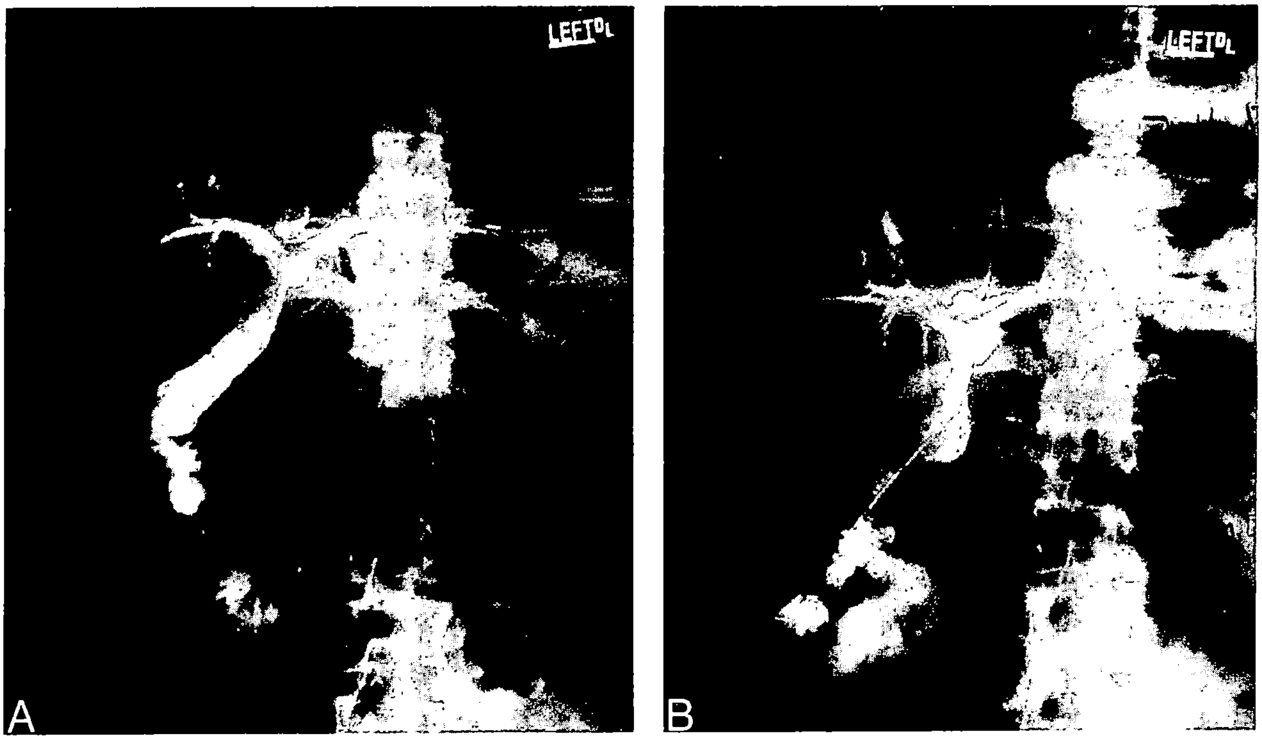
### *Rejection*

Of 123 grafts initial immunosuppression was CsA and methylprednisolone (61 grafts); CsA, methylprednisolone and azathioprine (48); OKT3, methylprednisolone and azathioprine (12); and OKT3, methylprednisolone, azathioprine, and CsA (2 grafts). There was no difference in graft survival for initial dual or triple immunosuppression (32% and 33%, respectively). Of the 82 surviving patients, 52 are currently receiving triple maintenance therapy. The mean steroid dose is 0.24 ± 0.18 mg/kg, and the mean CsA dose is 13.5 ± 11.2 mg/kg. There is no significant difference in either steroid or CsA dose for patients on dual or triple immunosuppression.

### *Treatment of Rejection*

A total of 94 grafts surviving more than 7 days required single or multiple steroid boluses for clinically suspected and/or biopsy-proved rejection. The first steroid bolus was unsuccessful in normalizing liver function in 38 grafts (40%). Ultimate graft survival rate was only 47% in this group, with a patient survival rate of 72%. Of these 38 grafts, 12 were treated with OKT3, 9 patients developed systemic sepsis following the steroid bolus, 5 had later biopsy evidence of vanishing bile duct syndrome, and 4 suffered a hyperacutelike rejection episode.

Of 13 patients requiring more than three steroid boluses, liver function eventually returned to normal in six. Four required retransplantation and three have chronically abnormal liver function.



FIGS. 7A and B. Biliary stricture before (A) and after (B) transhepatic balloon dilatation.

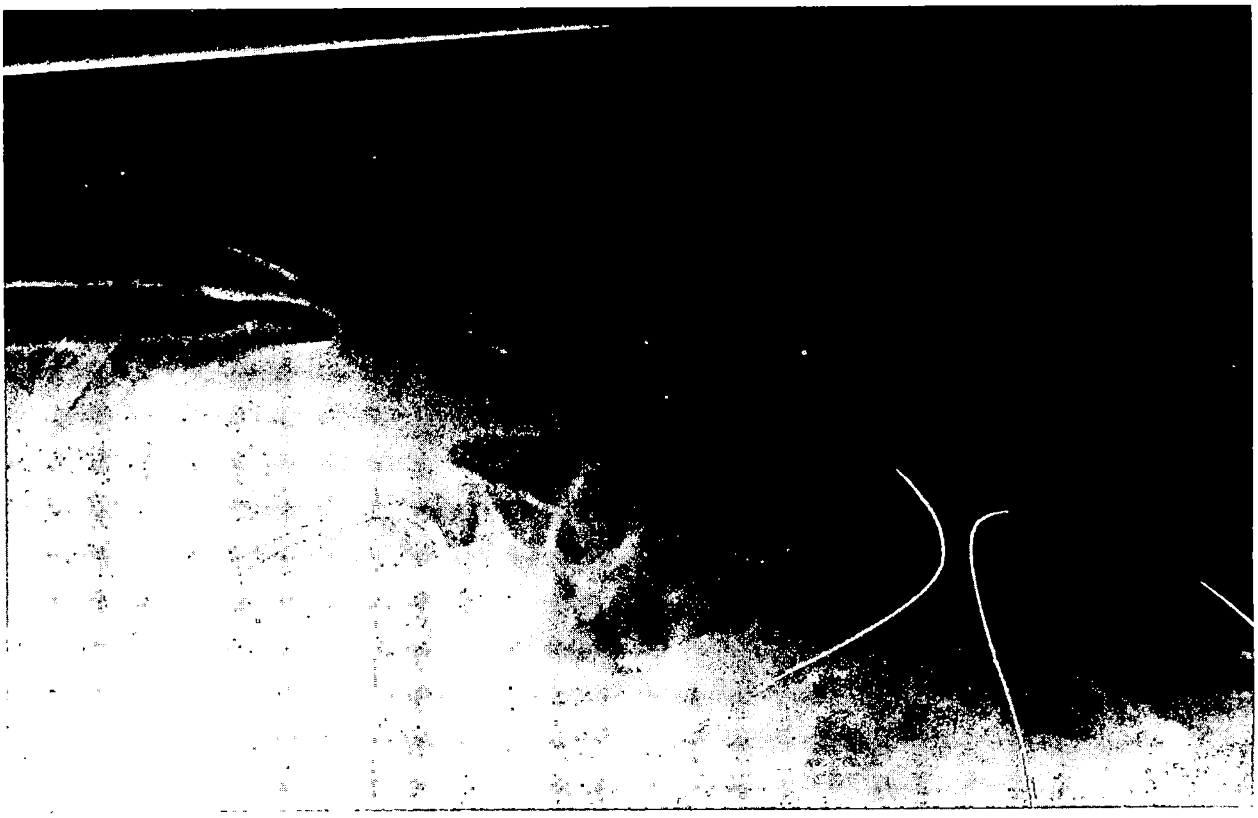


FIG. 8. Transtable lateral abdominal x-ray showing free intraperitoneal air in a patient with intestinal perforation.

Twelve patients received prophylactic OKT3. Early rejection was prevented in two patients, but there was no effect on the occurrence of late rejection. Five patients required later treatment with OKT3 for rejection, and normal liver function was achieved in four of them.

OKT3 was used to treat 43 episodes of rejection in 39 patients. Two patients received two courses of OKT3, and one patient was treated on three occasions. There was a 79% success rate in reversing rejection with OKT3.

### *Current Graft Function*

Liver function was graded in the 82 survivors according to serum transaminases and serum bilirubin. Seventy-eight per cent had normal transaminases and bilirubin, 12% had elevated transaminases (more than 200 mg/dL) and normal bilirubin, and 10% had both elevated transaminases and bilirubin.

### *Retransplantation*

Retransplantation was performed 21 times in 19 patients (18%), with a survival rate of 58%, and two patients received a third liver. Indications for retransplantation were HAT, rejection, primary nonfunction, and ischemia (Table 2).

Survival of patients retransplanted for HAT, rejection, primary nonfunction, and ischemia were 82%, 43%, 0%, and 100%, respectively.

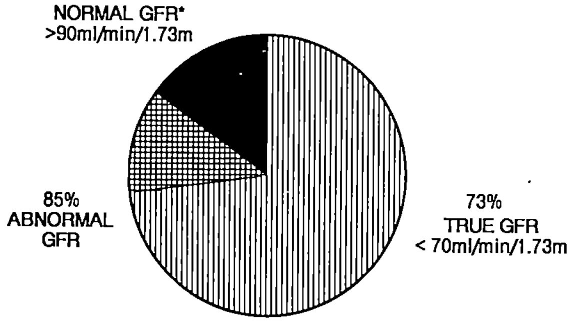
TABLE 2. *Retransplantation*

| OLT# | Indication | Outcome |
|---|---|---|
| 16 | Rejection | Dead |
| 21 | Rejection | Alive |
| 25 | Chronic rejection | Alive |
| 26 | HAT | Dead |
| 36 | #1 HAT<br>#2 HAT | Alive |
| 79 | HAT | Alive |
| 80 | HAT | Alive |
| 91 | Ischemia | Alive |
| 101 | Primary NF | Dead |
| 116 | HAT | Alive |
| 123 | Primary NF | Dead |
| 128 | HAT | Alive |
| 143 | Chronic Rejection | Dead |
| 161 | HAT | Dead |
| 162 | HAT | Alive |
| 169 | Rejection | Dead |
| 186 | HAT | Alive |
| 203 | #1 HAT<br>#2 Chronic rejection | Alive |
| 216 | Rejection | Dead |

HAT, hepatic artery thrombosis.
NF, nonfunction.

## Discussion

Human orthotopic liver transplantation has its foundations in the treatment of children, and the first successful human OLT was performed in a 19-month-old child with hepatocellular carcinoma in 1967.[5] This operation, although only successful in the short term, represented a pioneering effort and defined a new field of endeavor. One-year survival rates before 1980 were 30% to 40%,[6] but with the clinical use of cyclosporine and improved technical, anesthetic, and postoperative care, the 1-year survival rate is now 70% in most centers. Because of the improved results, the National Institutes of Health convened a consensus conference in 1983 and concluded that liver transplantation should be considered as the definitive therapy for various forms of end-stage liver in both adults and children.[7]



*Pts with normal GFR had significantly lower CyA levels

FIG. 9. True GFR measurements in patients receiving CsA for more than 1 year. Normal GFR in 15% of patients.

Although pediatric experience continues to increase, most liver transplants in this country are in adults. Fewer than 12 centers performing OLT have transplanted large numbers of children. We report a consecutive series of 123 pediatric liver transplants, which represents approximately 39% of our total liver transplant experience through December 1988.

Biliary atresia is the most common indication for pediatric liver transplantation and was the diagnosis in 47% of our patients. The surgical treatment of 'uncorrectable' biliary atresia was introduced in 1959 with description of the hepatoenterostomy operation by Kasai and Suzuki.[8] Portoenterostomy remains the preferred initial procedure in patients with extrahepatic biliary atresia, and it should be performed within 8 to 10 weeks of life for optimal results.[9] Even when bile drainage is successful, many patients will develop progressive cholestasis and cirrhosis. We believe that patients with failure of the first portoenterostomy should be referred for OLT, rather than undergo repeated attempts to achieve drainage, unless a clear mechanical obstruction can be demonstrated before operation. Not only have subsequent attempts at correction of a failed Kasai procedure been uniformly unsuccessful[10,11] but these reoperations increase the technical hazards of liver transplantation substantially. Such patients have greater blood loss and risk of infections after OLT, and they accounted for all four cases of bowel perforation in this series. Survival after OLT in biliary atresia patients is usually less than that for childhood metabolic diseases, with rates of 64% to 75% reported.[12,13] This is the consequence of technical difficulties following previous operations, smaller size of patients, and more advanced portal hypertension and synthetic failure.

Although the recipient hepatectomy in children may be an easier technical procedure than in adults, the infant with biliary atresia and multiple revisional operations represents a formidable challenge. Technical considerations include approach to the recipient hepatectomy and meticulous construction of vascular and biliary anastomoses. Our HAT incidence of 13% and biliary complication rate of 8% are comparable to recent reports of HAT rates of 7.4% to 33%[14–16] and biliary complications of 5% to 20%[14,17] in pediatric patients. Hepatic arterial thrombosis is a devastating complication, and at our institution, virtually all cases have occurred in the pediatric population. Hepatic arterial thrombosis must be suspected at the first sign of liver dysfunction, even in the early postoperative period. The definitive diagnosis is made with Doppler ultrasound examination or with angiography. Retransplantation is always required for early HAT, although 25% of our patients in which HAT occurred more than 2 weeks after operation are well but receiving long-term antibiotics with functioning grafts.

There is no role for expectant management of biliary complications because undrained bile collections become infected and uncorrected leaks often heal with strictures. Aggressive surgical and radiologic intervention with anastomotic repair or stenting is required and was performed in all eight of the biliary leaks that occurred in this series.

The immunosuppressive regimen used in children at UCLA has undergone several modifications since 1984. Currently triple induction and maintenance immunosuppression with cyclosporine A, corticosteroids, and azathioprine is used. Acute allograft rejection, occurring in approximately 70% of patients, usually can be treated successfully. Two corticosteroid boluses of 30 mg/kg were used as the initial treatment of acute allograft rejection and were successful in normalizing liver function in 60% of grafts treated. Partial or nonresponders receive repeated boluses. Based on our experience, we found that failure to control rejection with two to three steroid cycles is an indication for OKT3. The successful use of OKT3 for steroid-resistant rejection, as prophylaxis, and as first-line treatment of rejection has been reported by several centers.[18–22] The largest experience has been with treatment of rejection. Gordon et al.[22] reported the use of OKT3 to treat acute rejection in 130 OLTs. They found significantly lower retransplantation rates and improved 1-year graft survival as compared to historical controls who were transplanted under cyclosporine and steroids, with steroid or ALG treatment for acute rejection. Cosimi[23] reported a randomized trial comparing OKT3 and steroids in the treatment of rejection that had failed one or two boluses of methylprednisolone. The success of reversing rejection was 73% with OKT3 *versus* 23% for the steroids. We currently reserve OKT3 for treatment of rejection in patients who do not respond to steroid boluses or as first-line immunosuppression for patients with renal failure when cyclosporine is contraindicated. Measurement of the percentage of CD3+ cells is used to guide OKT3 therapy. Our results demonstrate the effectiveness of OKT3, with a 79% success rate in reversing steroid-resistant rejection.

Chronic use of immunosuppression in the child is fraught with serious complications. Infection occurred in two thirds of these patients and contributed to death in 62%. *De novo* malignancy was seen in only one child and responded to decrease in the cyclosporine dosage plus chemotherapy. Renal dysfunction is of significant concern and is measurable as a decrease of GFR after 1 year. These problems underscore the need for close monitoring of immunosuppression and development of less toxic drugs. Future improvements in immunosuppression lie in the identification of markers that predict rejection reliably and in the development of new agents with a better therapeutic index.

Analysis of the causes of death in this series (Table 1) shows that sepsis was a major or contributing factor in 13 of the 21 deaths (62%), a figure similar to the 65% rate reported by Andrews.[24] Causes of death among the subgroup of ABO unidentical patients is similar to that of the entire series, with sepsis being a major factor in 67% of the deaths among the ABO unidentical patients. No positive influence was seen on positive cross-match or HLA matching. It is probable that these patients fared worse because of their generally poorer preoperative condition.

Eighty-six per cent of all deaths occurred within 5 months of transplantation and only one death occurred more than 1 year after transplantation. Long-term survival has been excellent, with a 77% 5-year survival rate. These results are comparable to the 73%[24] and 86% rates[25] reported at 3 years and 2 years, respectively, by other centers.

As stated, no reduced-size liver grafts were used in this series. There have been deaths of patients on our waiting list that, in some cases, were due to lack of a suitable donor, but the rate is a relatively low 10%, which is comparable to the 4%[26] and 14%[27] rates reported by groups active in the transplantation of reduced-size grafts. As the activity of centers performing pediatric OLTs increase and donors become more scarce, the need for reduced-size liver transplantation undoubtedly will increase.

The experience reported herein supports the current concept that OLT is the treatment of choice for end-stage liver disease in children. The procedure can be performed with acceptable morbidity and mortality rates, and excellent quality of life may be anticipated for most patients. Currently all of our school-age survivors are able to attend school. A survival rate of 77% at 5 years for a disease process that would otherwise be uniformly fatal gives families a renewed hope that their children will be able to lead normal lives. Improved results are anticipated with greater availability of donor organs, earlier transplantation of patients on the waiting list, and development of more specific, less toxic immunosuppression.

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## References

1. Starzl TE, Marchiaro TL, Von Kaulla K, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963; 117:659–676.
2. Hiatt JR, Ament ME, Berquist WJ, et al. Pediatric liver transplantation at UCLA. Transplantation Proceedings 1987; 19:3282–3288.
3. Busuttil RW, Colonna JO II, Hiatt JR, et al. The first 100 liver transplants at UCLA. Ann Surg 1987; 206:387–402.
4. Quinones-Baldrich WJ, Memsic L, Ramming K, et al. Branch patch technique for arterialization of hepatic grafts. Surg Gynecol Obstet 1986; 162:488–499.
5. Starzl TE, Groth CT, Brettschneider L, et al. Orthotopic homotransplantation of the human liver. Ann Surg 1968; 168:392–415.
6. Starzl TE, Iwatsuki S, Van Diel D, et al. Evolution of liver transplantation. Hepatology 1982; 2:614–636.
7. NIH Consensus Development Conference Statement: Liver Transplantation. June 20–23, 1983. Hepatology 1984; 4:1075–1095.
8. Kasai M, Suzuki S. A New Operation for "Noncorrectable" biliary atresia: hepatic portoenterostomy. Shujutsu 1959; 13:733–739.
9. Ohi R, Hanamatsu M, Mochizaki I, et al. Progress in the treatment of biliary atresia. World J Surg 1985; 285–293.
10. Pettit BJ, Zitelli BJ, Rowe MI. Analysis of patients with biliary atresia coming to liver transplantation. J Pediatr Surg 1984; 19:770–785.
11. Altman RP. Results of reoperation for correction of extrahepatic biliary atresia. J Pediatr Surg 1979; 14:305–309.
12. Starzl TE, Esquivel C, Gordon R, et al. Pediatric liver transplantation. Transplant Proceedings 1987; 19:3230–3235.
13. Millis JM, Brems JJ, Hiatt JR, et al. Orthotopic liver transplantation for biliary atresia. Arch Surg 1988; 123:1237–1239.
14. Kalayoglu M, Stratta RJ, Sollinger HW, et al. Liver transplantation in infants and children. J Pediatr Surg 1989; 24:70–76.
15. Hoffer FA, Telle RL, Lillehei CW, et al. Infected bilomas and hepatic artery thrombosis in infant recipients of liver transplants. Radiology 1988; 169:435–438.
16. Mazzaferro V, Esquivel CO, Makowka L, et al. Hepatic artery thrombosis after pediatric liver transplantation—a medical or surgical event? Transplantation 1989; 47:971–977.
17. Stratta RJ, Wood PW, Langnas AN, et al. Diagnosis and treatment of biliary tract complication after liver transplantation. Surgery 1989; 106:675–684.
18. Colonna Jo II, Goldstein LI, Brems JJ, et al. A prospective study on the use of monoclonal anti-T3 cell antibody (OKT3) to treat steroid-resistant liver transplant rejection. Arch Surg 1987; 122: 1120–1123.
19. Kremer AB, Barnes L, Hirsch RL, et al. Orthoclone OKT3 monoclonal antibody reversal of hepatic and cardiac allograft rejection unresponsive to conventional immunosuppressive treatments. Transplant Proceedings 1987; 19:54057.
20. Goldstein G, Kremer AB, Barnes L, et al. OKT3 monoclonal antibody reversal of renal and hepatic rejection in pediatric patients. J Pediatr 1987; 111:1046–1050.
21. Esquivel CO, Fung JJ, Markus B, et al. OKT3 in the reversal of acute hepatic allograft rejection. Transplant Proceedings 1987; 19:2443–2446.
22. Gordon RD, Tzakis AG, Iwatsuki S, et al. Experience with orthoclone OKT3 monoclonal antibody in liver transplantation. Am J Kid Dis 1988; 11:141–144.
23. Cosimi AB, Cho SI, Delmonico FL, et al. A randomized clinical trial comparing OKT3 and steroids for treatment of hepatic allograft rejection. Transplantation 1987; 43:91–95.
24. Andrews WS, Wanek E, Fyock B, et al. Pediatric liver transplantation, a three year experience. J Pediatr Surg 1989; 24:77–82.
25. Otte JB, Yandza J, de Ville de Goyet J, et al. Pediatric liver transplantation, report on 52 patients with a 2 year survival of 86%. J Pediatr Surg 1988; 23:250–253.
26. Broelsch CE, Emond JC, Thistlewaite JR, et al. Liver transplantation, including the concept of reduced-size liver transplants in children. Ann Surg 1988; 208:410–420.
27. Otte JB, de Ville de Goyet J, Sokal E, et al. Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. Ann Surg 1990; 211: 146–157.

# Locally Recurrent Parathyroid Neoplasms as a Cause for Recurrent and Persistent Primary Hyperparathyroidism

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**Between 1982 and 1989, 145 patients underwent operations for persistent or recurrent primary hyperparathyroidism (HPT). At re-exploration, 15 patients (10.3%) were found to have locally recurrent parathyroid tumors (11 patients with adenoma and 4 with carcinoma). These 15 patients had 28 previous operations at outside institutions for HPT. Patients with locally recurrent HPT secondary to adenoma had a longer disease-free interval than patients with locally recurrent carcinoma. At the time of evaluation at the National Institutes of Health (NIH) for recurrent or persistent HPT, each patient was symptomatic and patients with carcinoma had significantly more symptoms and higher serum levels of calcium and parathyroid hormone than patients with adenoma. Locally recurrent parathyroid neoplasm was correctly localized by preoperative testing in 14 of 15 patients. These 15 patients underwent 18 reoperations at NIH for excision of locally recurrent parathyroid tumors. Following the final reoperation (two patients had more than one procedure), each patient had normal serum levels of calcium. In addition each patient remains biochemically cured (based on normal serum calcium level), with a median follow-up interval of 21 months. Local recurrence of parathyroid adenoma comprises a small but significant proportion of cases of recurrent or persistent HPT and can be indistinguishable from parathyroid carcinoma. Findings suggestive of carcinoma include shorter disease-free interval, higher serum levels of calcium and parathyroid hormone, and histologic appearance. Whether the locally recurrent parathyroid neoplasm is benign or malignant, aggressive surgery can control serum levels of calcium in these patients with acceptable rates of morbidity.**

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THE NUMBER OF patients with primary hyperparathyroidism (HPT) increased in the past two decades,[1] and consequently the number of failed operations for primary hyperparathyroidism also increased. The reasons for failed initial operations for primary hyperparathyroidism have been documented in several large clinical series[2–7] as well as in recent review articles.[8,9] Most patients who have unsuccessful operations for HPT have an adenoma that was not identified and excised at the initial procedure. Reasons for a missed adenoma include inexperience of the surgeon and unusual or ectopic locations such as intrathyroidal adenoma, intrathymic adenoma, or undescended adenoma.[2–9] A sizable proportion of patients with failed initial operations for primary hyperparathyroidism ultimately are demonstrated to have multiglandular disease or parathyroid hyperplasia. Initial operations in patients with hyperplasia may be unsuccessful because of failure to recognize the extent of disease, inadequate excision of parathyroid tissue, failure to identify supernumerary glands, or eventual regrowth of hyperplastic parathyroid remnants after an appropriate subtotal parathyroidectomy.[2–9]

Patients with parathyroid carcinoma comprise a small proportion of patients undergoing initial operation for HPT but have a marked propensity for local recurrence and metastases.[10] A major problem in these patients is failure to identify the carcinoma during operation and to perform an adequate resection of the pathologic parathyroid tissue with the adjacent lobe of the thyroid.[11,12]

Since 1982, as part of a large number of reoperations for persistent or recurrent HPT, a subgroup of patients with locally recurrent parathyroid neoplasms, including adenoma, has been identified. The local recurrence of pathologically proved benign parathyroid adenoma is rare

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but has been reported by others.[3,13] However many large comprehensive series of reoperations for HPT have not described the occurrence of locally recurrent parathyroid adenoma.[4–7]

Patients with locally recurrent parathyroid tumors present significant difficulties in surgical management. First the recurrent tumor is embedded in dense operative scar that increases the risk of surgical dissection and makes preoperative localization studies critical.[2,5,14] Second the fibrous appearance and contiguous invasive characteristics of a locally recurrent parathyroid adenoma may make it difficult to distinguish from a parathyroid carcinoma. Finally the ability to completely resect locally recurrent parathyroid tumors with the associated desmoplasia and local invasion may increase further the likelihood of recurrent laryngeal nerve injury, an event that is already five times more likely during reoperations for HPT.[8]

In the present study, all patients with locally recurrent parathyroid tumors during the past 7 years were evaluated. These patients were relegated into two groups identified by pathologic characteristics of the resected parathyroid tissue from the initial exploration as well as any reoperations. One group (four patients) is clearly identified as parathyroid carcinoma.[15] A second larger group (11 patients) is classified as either locally recurrent parathyroid adenoma or 'atypical adenoma' and, for this analysis, will be considered as adenoma. The clinical history, reoperative findings, and results from these patients will be described.

## Methods

Between July 1982 and April 1989, 145 patients with primary hyperparathyroidism underwent reoperation for either persistent or recurrent disease at the Clinical Center of the National Institutes of Health. Locally recurrent parathyroid tumors were found in 15 of 145 patients. The criterion used in this study to identify a patient with a locally recurrent parathyroid tumor as the cause of HPT was that operative records and pathologic analysis of specimens from previous and current operations for HPT indicated that a single abnormal gland located in the same anatomic area caused either persistent or recurrent HPT. Four patients had unequivocal pathologic features of parathyroid carcinoma such as mitoses, fibrous trabeculae, or local invasion of the capsule or vascular structures.[15] Nine patients had no apparent evidence of malignant characteristics and were thought to have locally recurrent parathyroid adenoma. Two patients had parathyroid glands with evidence of atypia but which could not be definitively identified as carcinoma and were classified as 'atypical adenomas.' For this analysis atypical adenomas were classified as adenoma.

Each patient underwent at least one previous neck exploration for primary hyperparathyroidism at another institution before referral to the NIH. Operative reports as well as pathology slides were obtained for each patient at the time of referral. The diagnosis of recurrent or persistent primary hyperparathyroidism was confirmed by serially elevated levels of serum calcium and parathyroid hormone in each patient. Persistent hyperparathyroidism is the documented presence of continued elevations of serum levels of parathyroid hormone and calcium following a neck exploration for HPT. Recurrent hyperparathyroidism is the presence of a documented period (lasting 6 months or longer) of normal serum levels of calcium and parathyroid hormone following an operation for HPT and then recurrent hypercalcemia and recurrent elevations of serum parathyroid hormone levels.[8] Indirect laryngoscopy was performed on each patient before and after reoperation at NIH to identify abnormalities of vocal cord function. Each patient underwent two or more noninvasive parathyroid imaging studies, including neck ultrasound, technetium-thallium nuclear medicine scan, computed tomography, or magnetic resonance imaging.[16–18] Based on whether the noninvasive studies identified an abnormal parathyroid gland, some of the patients had selective arteriography, including injections of the superior and inferior thyroid arteries and the internal mammary arteries.[19,20] If the arteriogram failed to definitively localize the lesion, then patients underwent selective venous catheterization of the neck and mediastinum for determination of parathyroid hormone concentration.[20]

Operative strategy for re-exploration was based on information from the previous operation at the outside institutions and the radiographic localizing studies from the NIH. Patients were re-explored through the standard transverse cervical incision. The parathyroid-thyroid area was approached *via* lateral dissection medial to the carotid sheath to avoid the previous midline surgical scar.[8,21] After operation all patients underwent repeat biochemical testing for serum calcium and parathyroid hormone levels. Long-term follow-up, including calcium levels, was obtained by either clinic visits or telephone report from the patient and the referring physician.

Statistical comparison of proportions was done by the Fisher's Exact test and means and SEM by independent Student's t test.

## Results

### *Patient Population*

Over a 7-year period 145 patients underwent re-exploration for HPT and 15 (10%) were found to have locally recurrent parathyroid tumor as determined by the present operative findings in conjunction with the information from the previous operative reports and pathology. The final pathology in the total patient population included 108 patients with parathyroid adenoma (74%), 33 patients with hyperplasia (23%), and 4 patients with parathyroid carcinoma (3%). The group of 15 patients with locally recurrent tumors consisted of the 4 patients with parathyroid carcinoma and 11 patients with parathyroid adenoma, including two patients with atypical adenoma. Therefore 11 of the total 108 patients (10%) with persistent or recurrent HPT due to an adenoma had locally recurrent parathyroid tumor following a previous operation.

### Results of Parathyroid Surgery Performed Elsewhere

The 15 patients found to have locally recurrent parathyroid tumor underwent a total of 28 previous operations at other institutions (Table 1). The group of four patients with parathyroid carcinoma had a total of eight operations with three of four patients having two or more previous neck explorations. The 11 patients with parathyroid adenoma underwent 29 parathyroid operations before admission to our institution. Six patients had a single previous neck exploration, while the other 5 patients had 14 previous neck operations, including 1 patient who underwent 5 previous procedures.

Following the original neck exploration for HPT, 4 of 4 (100%) patients with parathyroid carcinoma had recurrent HPT, indicating that each had at least a 6-month interval of normocalcemia followed by recurrent hypercalcemia (Fig. 1). Of the 11 patients with parathyroid adenoma and locally recurrent disease, 7 (64%) also had an interval of normocalcemia and 4 had persistent hypercalcemia (Fig. 1). Of the four patients with persistent HPT, each apparently had incomplete resection of abnormal parathyroid tissue that was eventually confirmed to be an adenoma on pathologic review at our institution.

TABLE 1. *Patient Characteristics and Results of Initial Operations at Other Institutions in Patients with Locally Recurrent Parathyroid Neoplasms*

| Characteristics | Parathyroid Cancer | Parathyroid Adenoma |
|---|---|---|
| n | 4 | 11 |
| Number of previous operations | 8 | 20 |
| Patients with >1 previous operation | 3 | 5 |
| Persistent disease* | 0 | 4 |
| Recurrent disease† | 4 | 7 |
| Initial pathology‡ | | |
| Adenoma | 2 | 11 |
| Hyperplasia | 1 | 0 |
| Carcinoma | 1 | 0 |

* Persistent disease is defined as recurrence of HPT within 6 months of the initial operation.

† Recurrent disease is defined as recurrence of HPT at least 6 months after the initial operation.

‡ Initial pathology was defined from records at referral institution.

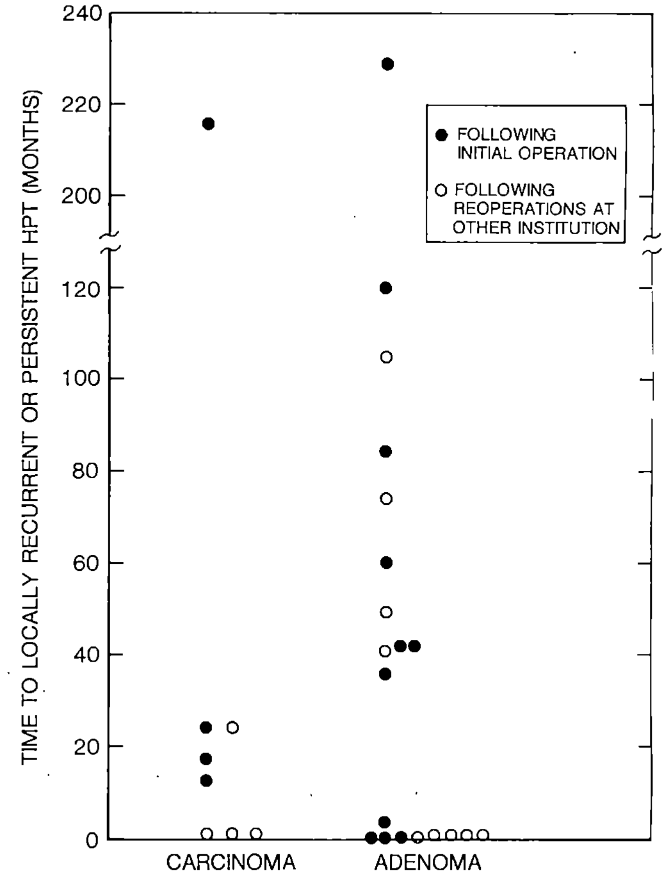

FIG. 1. Time to recurrent or persistent hyperparathyroidism (HPT) after either an initial operation (closed circle) or a reoperation (open circle) performed at an outside institution in patients with locally recurrent parathyroid neoplasms (adenoma and carcinoma). In general the patients with carcinoma recur earlier; however one patient with cancer did not recur until more than 200 months.

The disease-free interval (time to recurrent or persistent HPT) for patients with locally recurrent adenoma or carcinoma following operations at outside institutions tended to be shorter for patients with carcinoma, but there was some overlap (Fig. 1). Most patients with parathyroid cancer had recurrent hypercalcemia within 2 years. One patient did not develop recurrent disease until more than 16 years later (Fig. 1). Among the groups with recurrent HPT, patients had a significantly shorter disease-free interval from cancer than from adenoma ($p = 0.04$) (Fig. 2).

The pathology from outside operations is listed in Table 1. Tumors from each patient in both the adenoma and atypical adenoma groups was correctly classified as adenoma by the outside pathologist. Tumor from only one of four patients subsequently determined to have parathyroid carcinoma was initially identified as such. Two cancer patients were initially thought to have parathyroid adenoma and one to have hyperplasia. Two of these patients were correctly identified as having parathyroid car-

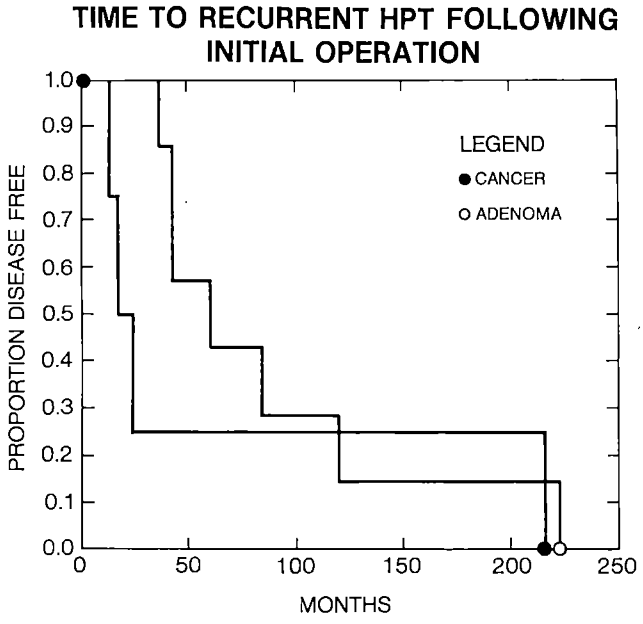

FIG. 2. Time to recurrent hyperparathyroidism (HPT) after a reoperation performed at an outside institution in patients with locally recurrent parathyroid tumors. Only patients with recurrent HPT (6-month interval of normalcalcemia) are included in this analysis. Patients with carcinoma (closed circles) developed recurrent hypercalcemia at a significantly shorter interval than patients with adenoma (p = 0.04).

cinoma at the time of re-exploration at another institution (Table 1).

*Symptoms and Laboratory and Localization Studies at NIH*

Each of the 15 patients with locally recurrent parathyroid tumor had at least one symptom attributable to HPT. Evaluating five categories of symptoms, patients with carcinoma had a greater percentage of complaints than patients with benign disease. The four patients with carcinoma had 75% of all potential symptoms, while adenoma patients had only 40% of the symptoms ($p < 0.01$) (Table 2).

Each patient had biochemical evidence of HPT with elevated serum levels of calcium and parathyroid hormone. Patients with cancer had a significantly greater serum level of calcium (7.2 ± 0.4 mEq/L) than patients with adenoma (5.8 ± 0.2 mEq/L, p = 0.003) (Table 2). Similarly patients with cancer had a significantly greater serum level of parathyroid hormone (1214% ± 574% more than normal) than patients with adenoma (268% ± 40% more than normal, p = 0.006) (Table 2). Twenty-four-hour urinary calcium levels were elevated in both the carcinoma and adenoma patients, but the absolute levels were similar in both groups. Serum phosphate levels were less than normal and again similar in both groups of patients. Each of the 4 carcinoma patients and 7 of 11 adenoma patients had serum levels of alkaline phosphatase greater than the upper limit of normal; however the mean levels were not different.

TABLE 2. *Symptoms and Biochemical Characteristics of Patients with Locally Recurrent Parathyroid Neoplasms*

| Symptoms/Characteristics | Cancer (n = 4) | Adenoma (n = 11) |
|---|---|---|
| Symptoms | | |
| Musculoskeletal (%) | 3 (75) | 4 (36) |
| Kidney (%) | 2 (50) | 7 (64) |
| GI (%) | 3 (75) | 2 (18) |
| Hypertension (%) | 3 (75) | 3 (27) |
| Constitutional (%) | 4 (100) | 6 (55) |
| Total (%) | 15/20 (75) | 22/55 (40)* |
| Laboratory | | |
| Calcium (mEq/L) | 7.2 + 0.4 | 5.8 ± 0.2† |
| Phosphate (mg/dl) | 2.1 + 0.2 | 2.1+ 0.1 |
| PTH (% > nl upper limit) | 1214 + 574 | 268 ± 4.0† |
| Urinary calcium (mEq/L/d) | 23.2 + 1.1 | 18.8 + 2.8 |
| Alkaline phosphatase (U/L) | 184 + 55 | 125 ± 13.2 |

* < carcinoma $p < 0.01$, Fisher's exact test.
† < carcinoma $p < 0.003$, Student's t test.

Fourteen of the fifteen patients with locally recurrent parathyroid disease had successful preoperative localization of tumors at the NIH (Table 3). Eight patients (53%) had definitive identification of the parathyroid tumor by the noninvasive tests, including three of the four cancer patients and about one half of the adenoma patients (Table 3). Seven patients went on to have selective angiography and three patients had selective venous sampling. One patient with an atypical adenoma had negative imaging studies and selective venous sampling.

Preoperative laryngoscopy identified unilateral vocal cord paralysis in 4 of the 15 patients. Each paralysis was thought to be secondary to operative injury to the recurrent laryngeal nerve on the basis of outside operative reports and the history of hoarseness immediately after surgery. Three of four recurrent laryngeal nerve injuries oc-

TABLE 3. *Preoperative Imaging Studies in Patients with Locally Recurrent Parathyroid Neoplasms*

| Study | Cancer | Adenoma | Both |
|---|---|---|---|
| Noninvasive Imaging Studies | | | |
| Ultrasound | 4/4* | 4/11 | 8/15 |
| CT scan | 3/4 | 5/11 | 8/15 |
| MRI scan | 1/2 | 1/7 | 2/9 |
| Tech-Thall scan | 1/4 | 4/11 | 5/15 |
| No. definite positive with noninvasive studies | 3/4 | 5/11 | 8/15 |
| Invasive Studies | | | |
| Angiogram | 1/1 | 4/6 | |
| Venous sampling | | 2/3 | 5/7 |
| Total positive with imaging studies | 4/4 | 10/11 | 14/15 |

* Number positive/number tested.

curred in patients with cancer (a 75% incidence), while only one patient with benign disease had a preoperative vocal cord palsy (9%; not significant).

### *Reoperations at the NIH*

*Adenoma.* The 11 patients with locally recurrent parathyroid adenoma underwent 12 reoperations at the NIH. Nine of eleven patients had a parathyroid mass excised from scar tissue in the exact same area that a pathologically proved single hypercellular gland was resected during a previous operation at an outside institution (patients 1 to 7, 10 and 11; Table 4). In each case the intraoperative diagnosis of a single abnormal parathyroid gland (tumor instead of hyperplasia) was established by either biopsy proof of a small additional normal parathyroid gland or an intraoperative decrease of urinary cyclic adenosine 3′, 5′-monophosphate (UcAMP) level after excision of a single abnormal gland.[22]

Resection of these locally recurrent parathyroid adenomas was difficult and tedious. One patient had the adenoma intimately intertwined with the recurrent laryngeal nerve where the nerve enters the larynx. Two patients (6 and 7) had hemoclips and suture material embedded in the parathyroid tumor. Two patients had diffuse seeding of muscle by a previously resected adenoma resulting in recurrent hyperparathyroidism (patients 8 and 9;, Table 4). One patient had a recognized resected parathyroid adenoma purposefully autografted into the left sternocleidomastoid muscle that required several previous reoperations at the outside institution to remove hypercellular parathyroid tissue from that muscle. After complete re-

TABLE 4. *Operative Findings and Follow-up in Patients with Locally Recurrent Parathyroid Neoplasms*

| Patient | Date of NIH Reoperation | NIH Reoperative Findings (pertinent outside operative findings) | Post-reoperative Length of Follow-up (mo) | Post-reoperation Recent Serum Calcium |
|---|---|---|---|---|
| | | Adenoma Patients | | |
| 1 | 1/27/83 | 25 × 11 × 10 mm. L mass in thyroid bed (L gland excised with L thyroid 10 years earlier) | 76 | Normal |
| 2 | 7/14/83 | 19 × 19 × 7 mm. R mass encased in scar (14 g. sup. adenoma excised 4 years earlier) | 70 | Normal |
| 3 | 11/17/83 | 17 × 13 × 8 mm. L sup. gland excised (1.7 g. L sup. adenoma excised with persistent disease) | 66 | Normal |
| 4 | 2/14/84 | 15 × 11 × 10 R mass in scar on the RLN (large R inf. adenoma excised 3 years earlier) | 63 | Normal |
| 5 | 5/20/85 | 13 × 9 × 6 mm. L T-E groove mass (2 cm. L. sup. adenoma excised 10 years earlier) | 49 | Normal |
| 6 | 11/21/88 | 18 × 15 × 10 mm. R gland in dense scar with hemoclip (R. sup. gland resected with persistent HPT) | 6 | Normal |
| 7 | 3/2/89 | 15 × 10 × 10 mm. R lower gland near suture material (R inf. gland resected with persistent HPT) | 3 | Normal |
| 8 | (i) 9/6/88 | 12 × 9 × 8 mm. R T-E groove mass (previous R sup. adenoma resected 18 years earlier) | 9 | Normal |
| | (ii) 9/12/88 | Subtotal thyroidectomy and R strap muscles for diffuse seeding of adenoma | | |
| 9 | 5/11/87 | Previous SCM autograft from adenoma, muscle and straps excised | 25 | Requires vitamin D and oral calcium |
| 10 | 2/3/86 | 30 × 20 × 18 mm. mass L of midline adherent to trachea 600 mg. R sup. adenoma removed 6 months earlier | 15 | Normal |
| 11 | 8/10/87 | L mass, thyroid, and RLN *en bloc* felt to be cancer (L inf adenoma exc. 7 years earlier) | 21 | Normal |
| | | Carcinoma Patients | | |
| 12 | (i) 8/21/86 | 2 nodules on left, thyroid, RLN *en bloc* (2 prior outside op initial dx hyperplasia then cancer at 2nd outside op) | 13 | Normal |
| | (ii) 9/30/87 | 2 nodules with muscle and thyroid | | |
| | (iii) 3/7/88 | L jugular nodes and muscle | | |
| 13 | 9/29/86 | R side mass, nodes and thyroid *en bloc* (2 previous outside operations, initial dx R sup. adenoma) | 33 | Requires vitamin D and calcium |
| 14 | 3/15/88 | R thyroid, nodes, and muscle *en bloc* (3 previous outside operations, initial op 9 g. cystic cancer) | 13 | Normal |
| 15 | 4/18/88 | 2 nodules R neck, piece of thyroid and scar (R inf. adenoma excised 18 years earlier) | 13 | Normal |

T-E, tracheoesophageal; RLN, recurrent laryngeal nerve; L, left; R, right; sup., superior; inf., inferior; HPT, primary hyperparathyroidism; SCM, sternocleidomastoid; op, operation; dx, diagnosis.

section of the sternocleidomastoid muscle at NIH, the patient was rendered hypocalcemic (patient 9; Table 4). Another patient required two reoperations performed at NIH during the same hospitalization (patient 8; Table 4). At the initial reoperation, a mass was resected from the right tracheoesophageal groove that was a locally recurrent parathyroid adenoma. There appeared to be marked desmoplasia throughout the area so several biopsies of adjacent strap muscles were obtained. Frozen section examination of these biopsies were negative, but permanent analysis demonstrated infiltration of the muscle with parathyroid tissue. The patient was returned to the operating room 6 days after the initial reoperation with a presumptive diagnosis of persistent HPT secondary to incompletely resected parathyroid cancer. Adjacent structures from the ipsilateral side of the neck (where the biopsies were taken) were completely resected including the thyroid, recurrent laryngeal nerve, and the adjacent strap muscle. These structures were invaded with a locally recurrent parathyroid adenoma. One patient (patient 10) with adenoma was thought to have cancer during the reoperation. The tumor mass was densely adherent to trachea requiring cautery excision of the mass from the trachea.

*Carcinoma.* The four patients with parathyroid carcinoma had a total of six parathyroid reoperations at NIH. One patient (patient 12) had three parathyroid reoperations during the course of 2 years to excise locally persistent or recurrent parathyroid cancer in lymph nodes, muscle, and thyroid tissue. In each patient with parathyroid cancer, all gross tumor was excised by aggressive local surgery and each patient was rendered disease free after the most recent reoperation as determined by lack of tumor on imaging studies and normal or low serum levels of calcium and parathyroid hormone. Three patients (patients 12, 13, and 14; Table 4) were known to have carcinoma and ipsilateral vocal cord paralysis before re-exploration and each underwent a radical excision, including recurrent nodules of cancer, surrounding musculature, lymph nodes, and ipsilateral thyroid. The fourth patient (15) had a more unusual history. This patient had excision of a right inferior parathyroid adenoma 18 years earlier with nothing unusual in the operative and pathology report and a long disease-free interval (Fig. 1). At re-exploration this patient had two distinct, firm nodules located on the same side as the previous abnormal parathyroid, with dense adherence to the adjacent thyroid. This area was re-excised and microscopic examination showed obvious local invasion that was diagnosed as parathyroid cancer.

### *Operative Results and Follow-up*

Each patient with adenoma and each patient with cancer was rendered disease free by the most recent reoperation performed at this institution. There was minimal morbidity associated with the operations at the NIH and no operative deaths. There were two new recurrent laryngeal nerve injuries documented by postoperative laryngoscopy. Each patient with cancer is currently disease free, but one patient (patient 12; Table 4) had a disease-free interval of 4 and 6 months following the first two reoperations performed here. He is disease free 13 months after his last reoperation. Two patients (patients 9 and 13; Table 4) have hypoparathyroidism requiring oral doses of 1,25-dihydroxy vitamin $D_3$ and calcium.

The median follow-up in the adenoma patients is 25 months (range, 3 to 76 months), and no patient developed recurrent hyperparathyroidism. The median follow-up in the carcinoma patients is 23 months (range, 13 to 32 months) and no patient developed recurrent hyperparathyroidism.

## Discussion

In our current series of 108 patients with persistent or recurrent HPT secondary to adenoma, more than 10% (11 patients) have local recurrence of a previously resected adenoma. These patients can present with either persistent or recurrent disease. Patients with parathyroid carcinoma also can develop locally recurrent tumor. The evidence presented here is consistent with the hypothesis that an adenoma can recur locally and cause recurrent HPT. Certainly a more common cause of recurrent HPT is hyperplasia[5,8,9,14] and although that diagnosis appears very unlikely, it cannot be excluded totally. In the future the findings described here may be substantiated further using polymerase chain reaction methods and formalin-fixed tissue to obtain accurate DNA 'fingerprints' of a tumor to unequivocally establish if the recurrence is derived from the same clone.

Parathyroid adenoma by definition is a discreet encapsulated lesion and surgical resection usually is curative. An adenoma can recur by violation of the capsule, incomplete excision leaving a portion of the gland *in situ*, or rupture of the capsule with spillage. Another potential mechanism is hyperfunction following implantation of the adenoma as an autograft. All three of these mechanisms are present in our current series but incomplete excision appears to account for most cases.

In 9 of 11 patients with adenoma, a single lesion surrounded by scar in the same general area as the initially excised adenoma was found, which may be an expected finding if a portion of an adenoma is left *in situ*. The size of the parathyroid remnant and the growth characteristics help determine the time to recurrent symptoms. If a large segment of the parathyroid adenoma remains after surgery, the patient may have no discernible change in calcium levels. Three patients had persistent HPT following the initial procedure despite identification and resection of abnormal parathyroid tissue. One explanation for incomplete resection of a parathyroid adenoma is bleeding in the operative field that may lead to failure to identify a sizable retained fragment of adenoma. The observation that two patients with persistent disease had a suture or a hemoclip on the retained adenoma fragment is consistent with this hypothesis. Another potential explanation for leaving a small fragment of adenoma during the initial resection is proximity to the recurrent laryngeal nerve. Four locally recurrent adenomas were in close proximity to the nerve.

The recurrence of HPT due to diffuse seeding of a wound following resection of a benign adenoma has been described previously.[3,13] One patient in the present study clearly met the criteria of this pattern, with multiple implants of hypercellular but nonmalignant parathyroid on the thyroid and strap muscles occurring 19 years after an initial resection. Two previous patients with seeding from a parathyroid adenoma described by Rattner et al.[13] had identical findings. Those two patients had disease-free intervals of 23 and 19 years after initial resections.

The recurrence of symptomatic HPT following autograft of a parathyroid adenoma is widely recognized.[23,24] Wide excision of the area of implantation in the present series resulted in apparent cure, but also resulted in hypoparathyroidism. We do not graft abnormal parathyroid tissue into the sternocleidomastoid muscle primarily for reasons exemplified by this patient. He required three additional neck operations to excise implanted parathyroid tissue (two were performed before referral to NIH). A forearm autograft site would result in a simpler operation if graft-dependent HPT arises.

Local recurrence is a hallmark of parathyroid carcinoma.[10] The four patients in the current series typify several of the well-documented features of this disease. At initial operation the diagnosis of parathyroid carcinoma was not made by either the operating surgeon or the pathologist in three of the four patients. The inability to recognize carcinoma in patients with HPT at their first operation and perform the necessary wide excision virtually ensures local recurrence due to microscopic local invasion.[10-12] The disease follows a pattern of recurrent biochemical abnormalities and symptoms with shorter disease-free intervals than seen in the case of recurrent adenoma (Figs. 1 and 2). However the benefits of aggressive local resection, even after failed initial and repeat operations noted by others,[11,12] was reinforced by our results with short-term success in each patient, including some who have had three or four neck explorations. One patient in our series had an unusual history of recurrent carcinoma with a disease-free interval of 18 years. The operative findings at re-exploration of two nodules embedded in previous scar argues for recurrent disease, although the possibility of a *de novo* carcinoma in a second gland cannot be precluded.

Locally recurrent benign adenoma would be considered a contradiction in terms by some investigators.[25] Local recurrence alone would be sufficient to acquire the status of carcinoma. However it appears clear that local recurrence can result by either incomplete resection or spillage of neoplasm, as found here. Furthermore the distinction between a locally recurrent adenoma due to incomplete excision and a locally recurrent carcinoma due to an intrinsically invasive lesion may be important in terms of prognosis. Some distinctions between locally recurrent benign and malignant lesions are evident in the patients presented. Patients with benign lesions have longer disease-free intervals than patients with malignant lesions (Fig. 2). At the time of recurrence, patients with carcinoma have more severe elevations of serum calcium and parathyroid hormone levels and more severe symptoms (Table 2). The presence of a vocal cord palsy is more indicative of a malignant lesion than a benign one (Table 2). At operation the distinction between recurrent adenoma and carcinoma are less clear secondary to distortion of tissue planes and tissue appearance by scarring.[13] However recurrent cancer is much more likely to present with either bulky disease or multiple grossly visible nodules compared to a single nodule in recurrent adenoma.

Despite the symptoms and signs described, there are no unequivocal clinical features that distinguish locally recurrent adenomas from carcinomas. The following approach is suggested for management of patients with recurrent or persistent HPT in whom an abnormal gland was reported to be resected previously. First obtain the pathology slides from the initial resection for review by an experienced pathologist. This review may identify as normal parathyroid tissue that was believed to be pathologic. In this case reoperation will focus on finding a missed parathyroid adenoma at a different site. On the other hand, the specimen may show evidence of carcinoma that would allow the work-up and surgery to focus on the ipsilateral side. If review of the pathology slides shows a hypercellular gland consistent with either adenoma or hyperplasia, the pathology should be reviewed further to determine if any normal parathyroid glands were biopsied. If not, then the possibility of parathyroid hyperplasia is most likely but a locally recurrent parathyroid adenoma is also possible.

The surgeon performing the reoperation must have a high index of suspicion for the presence and extent of locally recurrent parathyroid tumor. Most of these lesions were accurately localized before operation, but the extent and nature of the lesion can only be determined by palpation, visualization, and intraoperative ultrasonography. Intraopertive ultrasound can identify accurately the presence and extent of a parathyroid tumor amid the scar tissue.[26] Dense grayish infiltration of the muscle can be seen with locally recurrent parathyroid carcinoma and adenoma. If present and identified by biopsy, resection of the entire strap or sternocleidomastoid muscle should be performed. Adenomas generally do not invade into surrounding structures, but careful bloodless dissection is necessary to dissect out and excise the entire tumor. Care must be taken to identify the recurrent laryngeal nerve because often incompletely resected parathyroid adenomas will be adjacent to the nerve.

Locally recurrent parathyroid adenomas comprise a small but significant proportion of cases of recurrent or persistent hyperparathyroidism. These patients can have a single lesion that has regrown from an incompletely excised parathyroid adenoma, or less commonly, diffuse seeding of the previous operative field following operative spillage. It may be possible to preoperatively distinguish these patients from patients with parathyroid carcinoma by disease-free interval, level of serum calcium or PTH, and review of previous pathology slides. However, in some cases, the two diagnoses may be indistinguishable. Whatever the diagnosis, local, aggressive surgical reoperations can result in long-lasting cure. This approach is useful even in appropriately selected patients with multiple local recurrences of parathyroid carcinoma.

## References

1. Heath H, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. N Engl J Med 1980; 302:189–193.
2. Brennan MF, Norton JA. Reoperation for persistent and recurrent hyperparathyroidism. Ann Surg 1985; 201:40–44.
3. Cohn KH, Silen W. Lessons of parathyroid reoperations. Am J Surg 1982; 144:511–517.
4. Wang C. Parathyroid re-exploration. A clinical and pathological study of 112 cases. Ann Surg 1977; 186:140–145.
5. Grant CS, van Heerden JA, Charboneau JW, et al. Clinical management of persistent and/or recurrent primary hyperparathyroidism. World J Surg 1986; 10:555–565.
6. Granberg PO, Johansson G, Lindvall N, et al. Reoperation for primary hyperparathyroidism. Am J Surg 1982; 143:296–300.
7. Cheung PSY, Borgstrom A, Thompson NW. Strategy in reoperative surgery for hyperparathyroidism. Arch Surg 1989; 124:676–680.
8. Norton JA. Reoperative parathyroid surgery: indication, intraoperative decision-making and results. Prog Surg 1986; 18:133–145.
9. Remine SG. Management of recurrent or persistent hyperparathyroidism. *In* Nyhus LM, ed. Problems in General Surgery, Vol. 2. Philadelphia: JB Lippincott, 1985, pp 440–449.
10. Wang C, Gaz RD. Natural history of parathyroid carcinoma. Diagnosis, treatment, and results. Am J Surg 1985; 149:522–527.
11. Cohn K, Silverman M, Corrado J, Sedgewick C. Parathyroid carcinoma: the Lahey Clinic experience. Surgery 1985; 98:1095–1100.
12. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, et al. Parathyroid carcinoma: features and difficulties in diagnosis and management. Surgery 1983:94:906–915.
13. Rattner DW, Marrone GC, Kasdon E, Silen W. Recurrent hyperparathyroidism due to implantation of parathyroid tissue. Am J Surg 1985; 145:745–748.
14. Levin KE, Gooding GAW, Okerlund M, et al. Localizing studies in patients with persistent or recurrent hyperparathyroidism. Surgery 1987; 102:917–925.
15. Schantz A, Castleman B. Parathyroid carcinoma: a study of 70 cases. Cancer 1973; 31:600–605.
16. Miller DL, Doppman JL, Shawker TH, et al. Localization of parathyroid adenomas in patients who have undergone surgery. Part I. Noninvasive imaging methods. Radiology 1987; 162:133–137.
17. Skibber JM, Reynolds JC, Spiegel AM, et al. Computerized technetium/thallium scans and parathyroid reoperation. Surgery 85; 98:1077–1082.
18. Kneeland JB, Krubsack AJ, Lawson TL, et al. Enlarged parathyroid glands: high-resolution local coil MR imaging. Radiology 1987; 162:143–146.
19. Miller DL, Chang R, Doppman JL, Norton JA, et al. Localization of parathyroid adenomas: superselective DSA versus superselective conventional angiography. Radiology 1989; 170:1003–1006.
20. Miller DL, Doppman JL, Krudy AG, et al. Localization of parathyroid adenomas in patients who have undergone surgery. Part II. Invasive procedures. Radiology 1987; 162:138–141.
21. Saxe AW, Brennan MF. Strategy and technique of reoperative parathyroid surgery. Surgery 1981; 89:417–423.
22. Darling GE, Marx SJ, Spiegel AM, et al. Prospective analysis of intraoperative and postoperative urinary cyclic adenosine 3′, 5′-monophosphate levels to predict outcome of patients undergoing reoperations for primary hyperparathyroidism. Surgery 1988; 104:1128–1136.
23. Burk LB. Recurrent parathyroid adenoma: a case report. Surgery 1947; 21:95–101.
24. Brennan MF, Brown EM, Marx SJ, et al. Recurrent hyperparathyroidism from an autotransplanted parathyroid adenoma. N Engl J Med 1978; 299:1057–1059.
25. McKeown PP, McGarity WC, Sewell CW. Carcinoma of the parathyroid gland: is it overdiagnosed? A report of three cases. Am J Surg 1984; 147:292–298.
26. Kern KA, Shawker TH, Doppman JL, et al. The use of high-resolution ultrasound to locate parathyroid tumors during reoperations for primary hyperparathyroidism. World J Surg 1987; 11:579–585.

# Metabolic Changes in Patients Severely Affected by Tetanus

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**Metabolic changes in six severely affected tetanus patients suffering from characteristic labile hypertension (maximum systolic blood pressure greater than 200 mmHg, maximum diurnal change in systolic pressure greater than 100 mmHg) were investigated. Daily urinary excretion of urea nitrogen increased gradually from the onset of opisthotonus, reached a peak value (10.4 to 15.4 g/m$^2$) in 8 to 20 days, and decreased subsequently. Average cumulative excretion in 30 days reached 239.6 ± 32.7 g/m$^2$. Urine catecholamine excretion was elevated in each patient and remained elevated during this period. Plasma cortisol and glucagon concentrations were not increased markedly except in a case complicated other systemic bacterial infection. Increased protein catabolism in these patients could not be explained by the metabolic effects of 'stressed hormones' alone, and neurologic factors must be considered.**

SINCE LONG-TERM MECHANICAL respiratory support became available for tetanus patients, characteristic cardiovascular instability has been reported.[1,2] In these patients alternating arterial hypertension and hypotension persist for approximately 2 weeks. In the early phases, sudden cardiac arrest is a common complication, while later complications include renal failure and respiratory infections, which contribute to death in these patients.[3] Although many reports of this unique complication of severe tetanus exist, most are of sporadic cases. In addition, although its clinical features have been described as resulting from 'sympathetic nervous system overactivity,' only short periods of its clinical course have been investigated.[4-6] We treated six cases of tetanus with typical circulatory instability from 1983 to 1988 and investigated the metabolic features from onset of opisthotonus to recovery. We demonstrate characteristic metabolic features in these tetanus patients.

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## Materials

Six patients severely affected by tetanus revealing unusually labile hypertension (maximum systolic blood pressure greater than 200 mmHg, maximum diurnal change in systolic pressure greater than 100 mmHg) were studied. Patients' past medical histories were unremarkable for hypertension and other metabolic diseases. Individual patient characteristics are shown in Table 1.

## Methods

### *General Management*

All patients were given human tetanus immunoglobulin (5000 IU) at admission and benzylpenicillin potassium (20 million U/day) was administered for 7 to 10 days.

Sedation was achieved by intravenous administration of diazepam. Muscle paralysis was achieved by pancuronium bromide.

A ganglionic blocker and beta blocker were ineffective in controlling unstable blood pressure. In five of six patients, continuous spinal block using bupivacaine hydrochloride was needed during periods of severe circulatory instability. Although this was the most powerful way to stabilize labile hypertension, simultaneous catecholamine administration was necessary to counteract hypotension caused by the intrathecal local anesthetic.[7] During the 10 to 24 hours after the onset of spinal block, 0.3 to 0.4 μg/Kg/min norepinephrine or epinephrine was needed. Doses of catecholamines could be decreased to 0.1–0.02 μg/Kg/min subsequently. One patient was treated by continuous infusion of barbiturate (thiamylal sodium) without spinal block.

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TABLE 1. *Patient Characteristics*

| Case | Age (years) | Sex | Incubation Period (days) | Onset of Spasm (hours) | Onset of Labile Hypertension (days) | Ventilated Period (days) | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 75 | F | 10 | 23 | 6 | 42 | Survived |
| 2 | 32 | M | 7 | 48 | 7 | 26 | Survived |
| 3 | 60 | M | 8 | 72 | 10 | 37 | Survived |
| 4 | 41 | M | Unknown | 14 (days) | 19 | 36 | Survived |
| 5 | 33 | M | 7 | 10 | 2 | 30 | Survived |
| 6 | 39 | M | 10 | 48 | 5 | 32 | Survived |

Total parenteral nutrition was used in all patients. Steady nutritional supplementation was achieved within 5 days of admission. Patients received glucose (250 to 300 g/m$^2$), 250 mL of a 10% lipid emulsion, amino acids (5.0 to 6.4 g/m$^2$) with electrolytes, and other micronutrients continuously.

### *Sample Analysis*

Twenty-four-hour urine specimens were collected in bottles containing 20 mL 6N hydrochloric acid for estimation of catecholamine excretion. Epinephrine and norepinephrine levels were determined by high-performance liquid chromatography using fluorometric detection.[8]

Blood samples for cortisol levels were measured in serum by radioimmunoassay.[9] Blood samples for glucagon levels were taken in chilled tubes containing disodium salt of ethylenediaminetetraacetic acid and trasylol to minimize proteolytic degradation. Plasma glucagon concentration was determined by radioimmunoassay.[10]

The urea nitrogen content in 24-hour urine specimens was measured by routine examination in the central laboratory for clinical investigation in our hospital using specific enzyme methods.

## Results

The daily urine urea nitrogen (UUN) excretion of six patients is plotted from the beginning of mechanical ventilation (Fig. 1). With the exception of one patient (case 4), UUN excretion progressively increased, reaching peak values in 8 to 15 days. In case 4 the peak UUN excretion was delayed to 20 days after the onset of mechanical ventilation. In this case the patient underwent surgical drainage of left-sided retroperitoneal abscess cavity on day 30. This patient did not have history of trauma, and *Clostridium tetani* was suspected to come from the colon. The

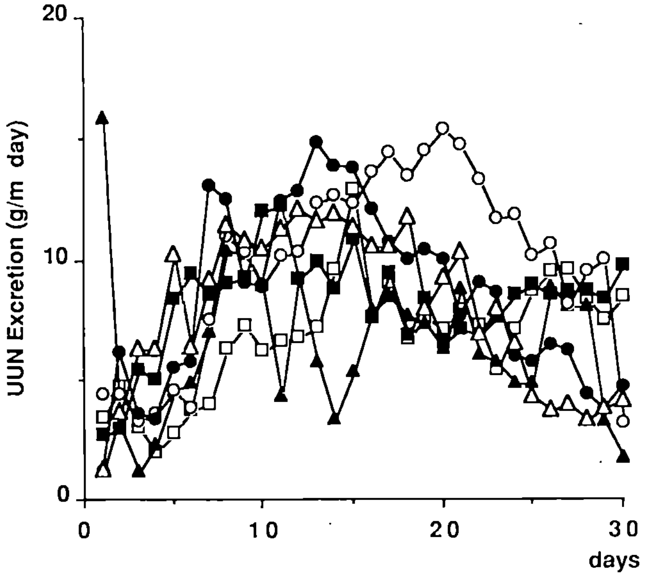

FIG. 1. Changes in daily urine urea nitrogen excretion (UUN) for each patient (case 1: □, case 2: ▲, case 3: ■, case 4: ○, case 5: ●, case 6: △). Values are expressed in grams of nitrogen per square meter of patient's body-surface area.

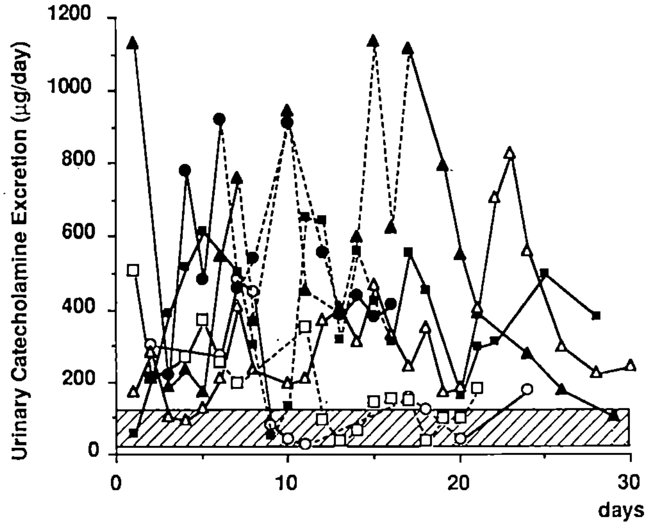

FIG. 2. Changes in daily excretion of catecholamines (epinephrine and norepinephrine) for each patient (case 1: □, case 2: ▲, case 3: ■, case 4: ○, case 5: ●, case 6: △). Dotted lines represent periods of continuous spinal anesthesia. During these periods, small amounts of catecholamine were infused continuously to maintain blood pressure. The shaded area indicates the normal range.

peak excretion values of these six cases ranged from 10.4 to 15.4 g/m$^2$ and cumulative 30-day excretion reached 239.6 ± 32.7 g/m$^2$.

Daily measurements of catabolic hormones were performed. Urine catecholamine excretion increased markedly in each patients (Fig. 2). The excretion of norepinephrine was increased markedly (Fig. 3). During periods of labile hypertention, some patients received continuous spinal block and small amount of catecholamine simultaneously. However urine catecholamine excretion remained increased in these patients after the cessation of continuous spinal block. In addition, in one patient (case 6) not receiving continuous spinal block, urine catecholamine excretion also was increased excessively.

Serum cortisol levels were measured in three of six patients. In contrast to urinary catecholamine increase, serum cortisol concentration was not increased. Serum cortisol levels remained in the normal range during the whole course, except in case 4, in which the patient suffered sepsis and needed surgery for a retroperitoneal abscess (Fig. 4).

Plasma glucagon concentrations also were measured in three cases. Glucagon levels did not increase excessively, except in case 4 (Fig. 5).

## Discussion

One important observation of our study is the increased urinary nitrogen excretion in our patients. Urine urea nitrogen excretion increased from the onset of ventilation, reached a peak (at 8 to 20 days), and then decreased gradually, with levels remaining high for 1 month. These patterns are different from those of traumatized or postoperative patients. In traumatized and postoperative patients, the peak day comes earlier and the increase in UUN excretion is limited to a shorter period, barring complications.[11]

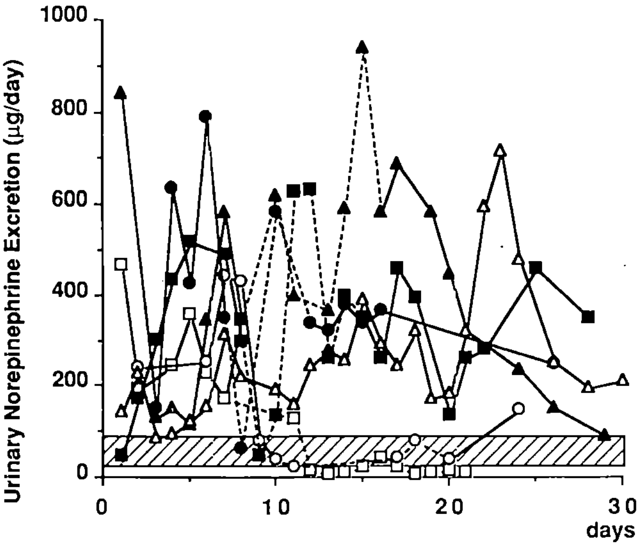

FIG. 3. Changes in daily urinary excretion of norepinephrine for each patient (case 1: □, case 2: ▲, case 3: ■, case 4: ○, case 5: ●, case 6: △). Dotted lines represent periods of continuous spinal anesthesia. During these periods, small amounts of catecholamine were needed to avoid hypotention. The shaded area indicates normal range.

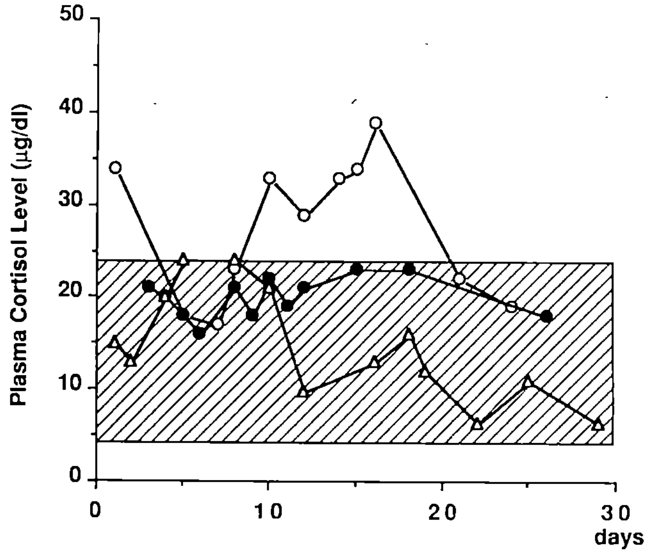

FIG. 4. Changes in plasma cortisol concentration for three patients (case 4: ○, case 5: ●, case 6: △). The shaded area indicates normal range.

To investigate this catabolic response, three 'stress' hormones were measured in these patients. Urinary catecholamine excretion increased markedly. Increases in circulatory catecholamines were observed also in traumatized and postoperative patients. However these increased levels decreased within 1 day after injury.[12] In our tetanus patients not only did urinary catecholamine excretion increase to the level of patients with pheochom-

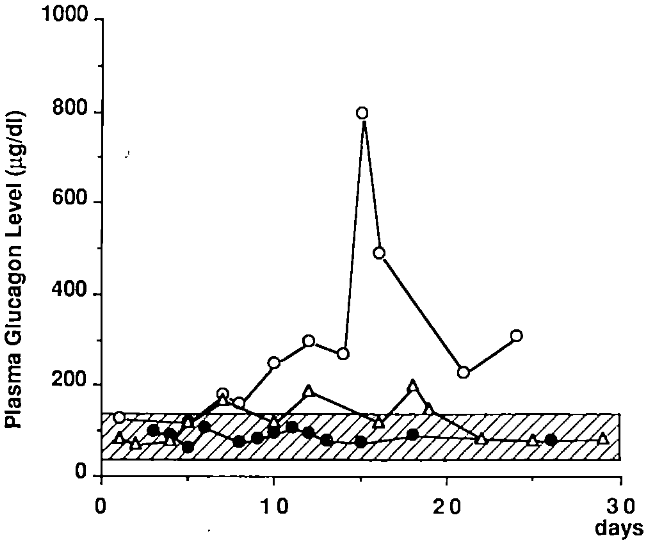

FIG. 5. Changes in plasma glucagon concentration for three patients (case 4: ○, case 5: ●, case 6: △). The shaded area indicates normal range.

ocytoma but this increase was also sustained for 3 weeks or more without recurrent injury.

In contrast to the increases in chatecholamine excretion, plasma cortisol levels were not elevated during the whole course. A mean plasma cortisol concentration of approximately 40 $\mu$g/dL was observed by Stoner[13] following moderately severe injury. In our patients plasma cortisol concentrations did not exceed the upper border of morning levels found in normal subjects, except in case 4. As noted this was not considered to be a simple case of tetanus alone.

Plasma glucagon concentrations were not remarkably increased, except case 4. In cases of traumatized or surgically stressed patients, plasma glucagon levels are markedly elevated.

These results distinguish the endocrinologic features of tetanus patients from those of other stressed patients and raises questions about current theoretical contructs of the 'catabolic response.'

The first question regards the role of catecholamine in the post-traumatic metabolic course. Some have posited a theoretical link between catecholamine and other hormones in which catecholamines stimulate the supraoptic nuclei to the production of ACTH that leads to a secondary increase in cortisol production by the adrenal cortex.[14] It has been speculated also that increased glucagon production is under the influence of catecholamines. In our patients, however, excessively secreted catecholamines did not induce elevations in plasma cortisol or glucagon, at any time. This suggests that increased catecholamine secretion does not necessarily trigger other 'stress' hormones.

A second question regards the relationship between protein catabolism and 'stressed' hormones. Studies of hormonal infusion have investigated the relationship of various hormones to nitrogen loss. Cortisol and glucagon have been considered to be the important hormones responsible for hormone mediated nitrogen loss.[15–17] Bessey et al.[18] emphasize synergistic interactions between the three 'stress hormones.' These studies suggest that nitrogen loss is in response to more than just catecholamine elevation. The duration and magnitude of nitrogen loss in our patients cannot be explained by a change in counterregulatory hormones.

The plasma catecholamine level in explaining this unique metabolic change must be considered. In our patients the level of catecholamine was extremely elevated and is not comparable to the level of other states or hormonal infusion study. In addition we could speculate also about the influence of neurologic factor. The clinical features of these patients are essentially attributable to a derangement of function of neuron caused by tetanus toxin.[19] Although it is difficult to estimate the effect of the neurologic factors on metabolic response quantitatively, results in our patients suggest that factors other than endocrinologic, possibly neurologic ones influenced protein catabolism. Case 4 was not a case of simple tetanus but rather was complicated by severe sepsis. The metabolic feature of this case may be explained by the additive effect of tetanus and general stress caused by infection.

The metabolic changes in our tetanus patients are different from those of other stress states. They are characterized by marked and sustained elevations in catecholamine secretion without increases in plasma cortisol or glucagon levels. In these patients UUN excretion is markedly increased for long periods of time. Increased protein catabolism was not be explained by the metabolic effect of 'stressed hormones' alone, but neurologic factors must be considered as well.

## References

1. Kerr JH, Corbett JL, Prys-Roberts C, et al. Involvement of the sympathetic nervous system in tetanus: studies on 82 cases. Lancet 1968; ii:236–241.
2. Alfery DD, Rauscher LA. Tetanus: a review. Crit Care Med 1979; 7:176–181.
3. Heurich AE, Brust JCM, Richter RW. Management of urban tetanus. Med Clin North Am 1973; 57:1373–1381.
4. Benedict CR, Kerr JH. Assessment of sympathetic overactivity in tetanus. Br Med J 1977; 24:806.
5. Keilty SR, Gray RC, Dundee JW, McCullough H. Catecholamine levels in severe tetannus. Lancet 1968; ii:195.
6. Lieshout JJ, Wieling W, Romijin JA, Stam J. Hyperadrenergic syndrome with hypertention, hypotention, and myocardial necrosis in tetanus. Neth J Med 1988; 33:33–36.
7. Sugimoto H, Shibuya M, Uenishi M. et al. Long-term continuous spinal anesthesia in severe tetanus with autonomic disturbance. Klin Wochenschr 1987; 65:238–243.
8. Mori K. Automated analysis of biologic amines by high performance liquid chromatography with fluorometric detection. Tanpaku Kakusan Kouso 1981; 26:39–47.
9. Nishikawa T, Tamura Y, Kumagaya T. Studies on the determination of cortisol by gamma coat kit. Hormone to Rinsho 1980; 28: 471–476.
10. Yamada Y, Kobori K, Oshima H. Radioimmunoassay for pancreatic glucagon. Hormone to Rinsho 1980; 28:1115–1119.
11. Duke JH, Jørgensen SB, Broell JR, et al. Contribution of protein to caloric expenditure following injury. Surgery 68; 1970:168–174.
12. Davis CL, Newman RJ, Molyneux SG, Grahame-Smith DG. The relationship between plasma catecholamines and severity of injury in man. J Trauma 1984; 24:99–105.
13. Stoner HB, Barton RN, Little RA, Yates DW. Measuring the severity of injury. Br Med J 1977; 2:1247–1249.
14. Meguid MM, Brennan MF, Aoki TT, et al. Hormone-substrate interrelationships following trauma. Arch Surg 1974; 109:776–783.
15. Gelfand RA, Mattheus DW, Bier DM, Sherwin RS. Is the catabolic response to major stress mediated by couter-regulatory hormones? Clin Res 1983; 31:241(Abstr).
16. Parson W, Crispell KR, Ebbert A. Abnormalities in $N^{15}$ excretion rates after ingestion of tagged glycine in Cushing's syndrome and following ACTH administration. J Clin Invest 1952; 31:548–554.
17. Wolfe BM, Culebras JM, Aoki TT, et al. The effects of glucagon on protein metabolism in normal man. Surgery 1979; 86:248–257.
18. Bessey PQ, Watters SM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. Ann Surg 1984; 200:264–281.
19. Erdman G, Wiegard H, Wellhöner HH. Intraaxonal and extraaxonal transport of $^{125}$I-tetanus toxin in early local tetanus. Naunyn Schmiedebergs Arch Pharmacol 1975; 290:357–373.

# Congenital Tracheal Stenosis with Unilateral Pulmonary Agenesis

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**Congenital tracheal stenosis with unilateral pulmonary agenesis is a rare and frequent fatal combination. In an 8-year period, 5 infants (ages 2 to 6 months) with these anomalies were treated. The presenting signs and symptoms consisted of wheezing, stridor, and tachypnea and included frank respiratory failure requiring emergency therapy in several patients. The operative repair consisted of segmental resection and anastomosis in one patient, and rib-cartilage tracheoplasty in the other four. Two infants died, one of cerebral hypoxia, and the other of aortotracheal fistula. Long-term follow-up in the three survivors is satisfactory.**

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CONGENITAL TRACHEAL STENOSIS with unilateral pulmonary agenesis is a rare but well-known combination of anomalies. This combination generally is fatal, with only a few survivors of attempted repair having been reported. Because tracheal stenosis associated with solitary lung frequently involves a long tracheal segment, or even the entire trachea, simple excision and anastomosis have rarely been possible. In addition the rarity of the combination of malformations has limited the experience that any one center has accumulated.

In 1982 Kimura[1] described a new technique for the repair of congenital tracheal stenosis that involved the use of rib cartilage graft. Since then several successful cases have been reported using this technique. However most of these cases did not involve reconstruction of the trachea to a solitary lung. The present series details the use of rib cartilage graft tracheoplasty and other techniques in five infants with critical congenital tracheal stenosis and unilateral pulmonary agenesis.

## Materials and Methods

### *Patients*

In an 8-year period, 25 infants and children with congenital tracheal stenosis were managed with a variety of techniques. Within this group, 20 had normal bilateral lung development, while the remaining five infants had the combination of tracheal stenosis and unilateral agenesis. The latter five patients form the basis for this report.

The patients were 2 to 6 months old when the tracheal stenosis was first diagnosed. There were three boys and two girls. In three infants the unilateral pulmonary agenesis was found at the time of the discovery of tracheal stenosis, while two others had known pulmonary aplasia at birth and were being followed closely for the development of respiratory difficulties. In neither of these latter cases was a work-up performed at birth for tracheal stenosis.

The characteristics, signs, symptoms, and pulmonary and tracheal anomalies for each patient are shown in Table 1 and Figure 1. Generally the children with shorter stenoses (patients 1 and 2) presented with milder symptoms, although sufficiently significant to warrant work-up. It is interesting to note that these two patients were being treated for 'asthma' but had become refractory to bronchodilation therapy, which prompted further work-up. In contrast the three infants (patients 3, 4, and 5) with extensive tracheal stenosis involving long segments of the trachea presented in severe respiratory failure, with severe symptoms and markedly abnormal blood gases.

The work-up in each case consisted of a plain chest x-ray (Fig. 2) followed by computed tomography (CT) scan in three of the five cases (patients 1, 2, and 5). In patients 1 and 2, the CT scan was obtained before endotracheal intubation, while patient 5 was intubated for respiratory failure and deterioration of blood gases. Although helpful in aiding in the diagnosis of tracheal stenosis, the extent of the stenosis could not be assessed accurately with this

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TABLE 1. *Patient Characteristics*

| Patient Number | Age (mos)/ Sex | Symptoms and Signs | Initial Blood Gases $PO_2/pCO_2/pH$ (mmHg) | Pulmonary Anomaly | Location of Tracheal Anomaly |
|---|---|---|---|---|---|
| 1 | 6/F | Wheezing, tachypnea | 65/70/7.25 | Right agenesis | Cervical |
| 2 | 3/F | Stridor, tachypnea | 88/50/7.30 | Left agenesis | Cervical to lower trachea |
| 3 | 2/M | Respiratory failure | 55/120/6.95 | Right agenesis | Cervical to lung hilum |
| 4 | 2/M | Respiratory failure | 60/145/6.80 | Left agenesis | Vocal cords to lung hilum |
| 5 | 3/M | Severe wheezing, stridor, respiratory failure in 6 hours | 44/90/7.11 | Right agenesis | Cervical to lung hilum |

technique, thus limiting its usefulness. Tracheograms with dilute barium were performed in two cases, both at the time of bronchoscopy (Fig. 3).

Bronchoscopy was performed in each case, which resulted in acute deterioration in every child. The deterioration was manageable in cases 1 and 2 by the placement of a small (2.5 mm) endotracheal tube through the stenosis. This allowed short-term adequate ventilation in these two patients, and each underwent operative repair within 12 hours.

The three infants with extensive tracheal stenosis were more difficult to manage before repair. Patient 3 deteriorated rapidly after bronchoscopy and could not be ventilated. He underwent emergency thoracotomy for tracheal repair. Patient 5 was ventilated with a high pressure, high-rate respirator, which gave adequate blood gases for 6 hours, at which time he deteriorated and underwent urgent thoracotomy and tracheal repair.

Patient 4 had rapid deterioration after bronchoscopy at another hospital and was transferred in moribund condition. Because it was thought that he would not survive attempted repair, we elected to place him on extracorporeal membrane oxygenation (ECMO), and repaired his tracheal stenosis 48 hours later. Extracorporeal membrane oxygenation has been used extensively for newborn respiratory failure from other causes,[2] but its use in this setting has not, to our knowledge, been reported previously. Briefly, the technique of ECMO involved cannulation of the right jugular vein and carotid artery, after systemic heparinization. This allowed connection to an extracorporeal circulatory apparatus, consisting of a reservoir, roller pump, membrane oxygenator, and heat exchanger.[2] With the onset of ECMO, the patient stabilized and the blood gases rapidly returned to normal. The patient then underwent tracheal reconstruction while connected to the extracorporeal circuit and was later weaned from ECMO.

### Operative Technique

The operative repair of patient 1 consisted of segmental resection with end-to-end anastomosis. This was performed without cardiopulmonary bypass, by intubating the distal trachea after transection was completed (Fig. 4).

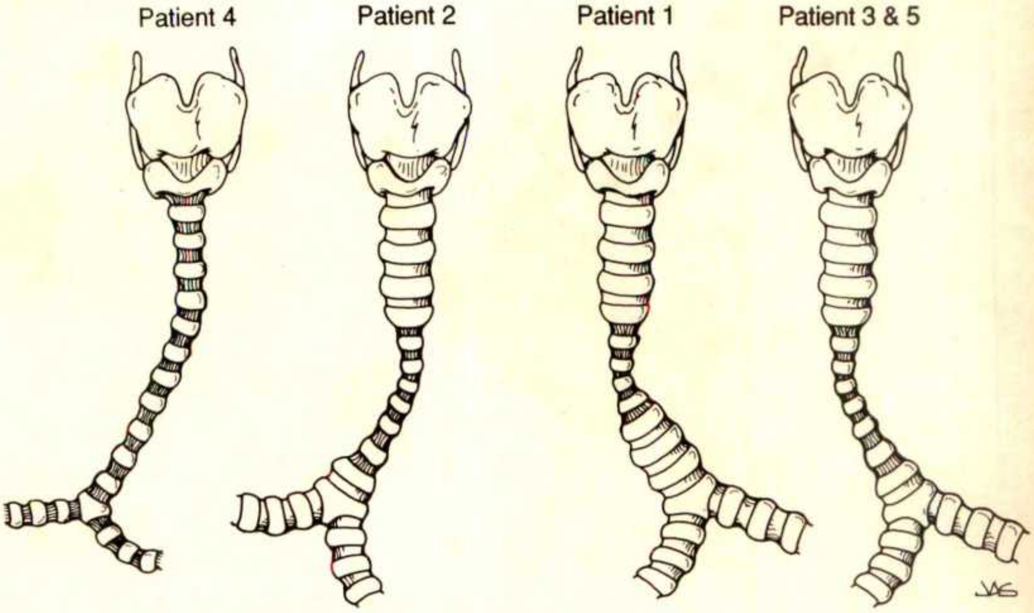

FIG. 1. Extent of stenosis in five infants with unilateral pulmonary agenesis and tracheal stenosis.

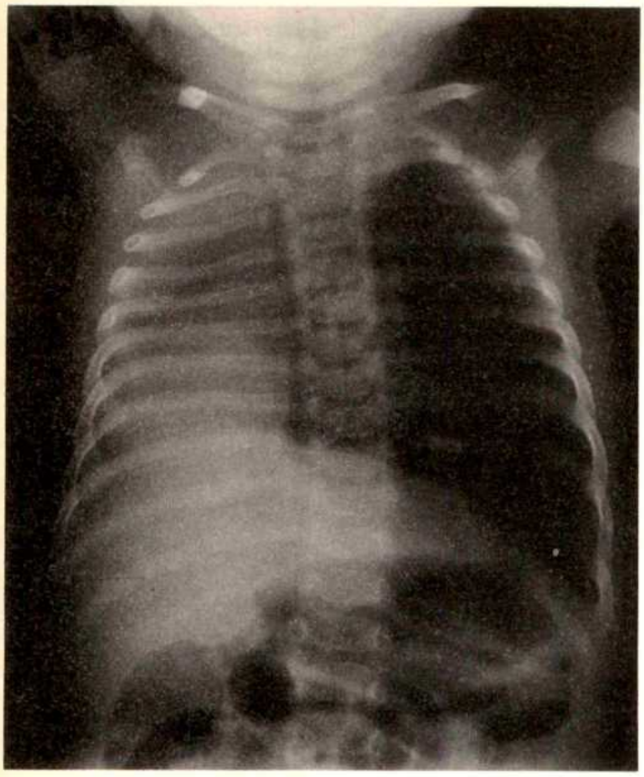

FIG. 2. Chest x-ray of an infant with tracheal stenosis and right pulmonary agenesis. Note hyperinflation of the left lung.

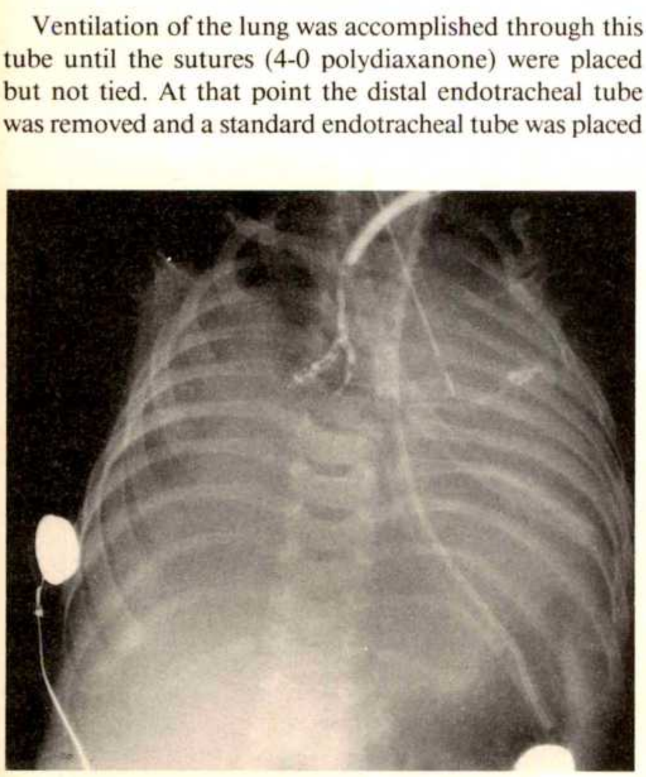

FIG. 3. Tracheogram in an infant with agenesis of the left lung and severe, diffuse tracheal stenosis to the hilum. Reconstruction with rib cartilage graft was successful.

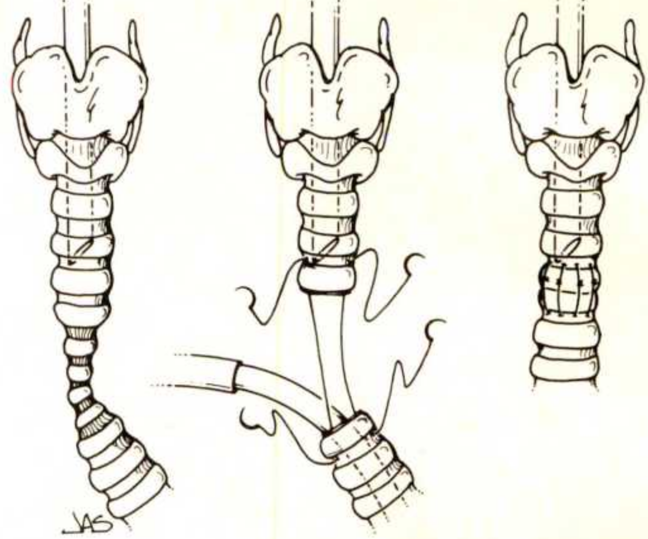

FIG. 4. Operative technique for patient 1. After resection of the narrow tracheal segment, the distal trachea was intubated while the anastomosis was performed. Ventilation was then resumed *via* an oral endotracheal tube.

Ventilation of the lung was accomplished through this tube until the sutures (4-0 polydiaxanone) were placed but not tied. At that point the distal endotracheal tube was removed and a standard endotracheal tube was placed through the vocal cords and advanced through the area of anastomosis, and ventilation was resumed through the oral endotracheal tube. The sutures were then tied.

The remaining patients, having more extensive lesions, required more complicated procedures. Rib cartilage tracheoplasty, using the technique of Kimura,[1] was performed without cardiopulmonary bypass in patients 2, 3 and 5, and with ECMO in patient 4. Briefly, the surgical procedure consists of exposure of the stenotic trachea through a transverse thoracic incision that transects the sternum at the third interspace. The great vessels are mobilized and retracted. The position of the heart in unilateral pulmonary agenesis is variable, but has not presented particular difficulties in tracheal exposure.

The trachea itself may not appear extremely abnormal externally. The trachea is gently palpated to ascertain the location of the distal end of the endotracheal tube, which has been positioned just above the most proximal area of narrowing. A rigid or small flexible bronchoscope can be used to aid in positioning the endotracheal tube. The anterior tracheal wall is opened longitudinally, beginning at the endotracheal tube and continuing distally until normal tracheal lumen is encountered. The endotracheal tube is advanced by the anesthesiologist as the trachea is opened. Frequently at this point the ventilation of the patient improves markedly, and the blood gases rapidly become normal (Fig. 5). With the endotracheal tube in place within the lumen, a graft of rib cartilage, harvested from the anterior chest wall, is cut coronally and fashioned to fit into the tracheal defect (Fig. 6), where it is sutured in place with interrupted 4-0 polydiaxanone or 4-0 prolene (Fig.

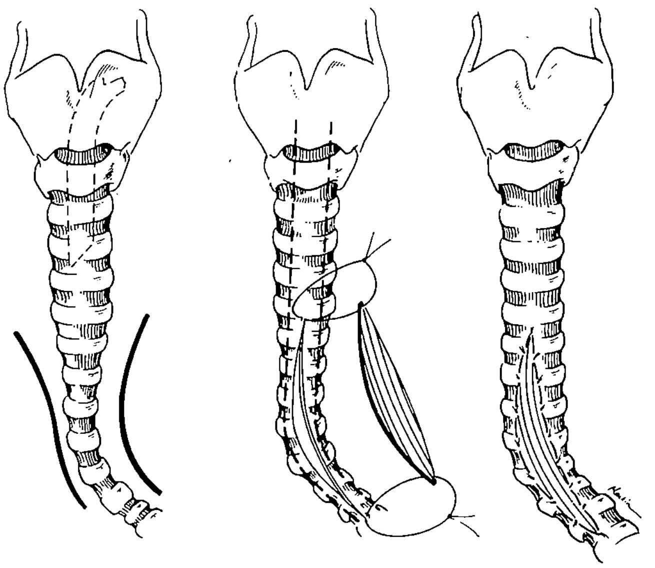

FIG. 5. Operative technique for rib cartilage graft tracheoplasty. After opening the narrow trachea anteriorly, the endotracheal tube is advanced and a graft of rib cartilage, prepared as in Figure 6, is sutured with interrupted monofilament sutures.

5). The perichondrium is excised with the cartilage, and the graft is placed with the perichondrium toward the lumen. In addition longitudinal, partial-thickness cuts are made in the nonperichondrium side of the cartilage to allow it to conform to a more natural tracheal shape (Fig. 6). The tube is left in place and converted to a tracheostomy tube in 7 to 10 days. Care is taken to keep the suture material in an extraluminal position because troublesome granulomas can form on suture material within the tracheal lumen. Before closure soft tissue (thymus) is interposed between the graft and any great vessels that it contacts.

Postoperative care consists of intubation, either by a nasotracheal tube or tracheostomy, and ventilator support, the latter of which is weaned over several days. On the seventh to tenth postoperative day, the child is returned to the operating room where bronchoscopy is performed using a rigid, ventilating bronchoscope (Stortz, Culver City, CA). In patient 1, in whom resection and end-to-end anastomosis were performed, the suture line was found to be well healed, without evidence of stenosis or infection, and thus the endotracheal tube was successfully removed at that time. In each case in which rib cartilage graft was used, the graft was seen to collapse into the airway lumen. Thus stenting of the graft was accomplished, first with an endotracheal tube-tracheostomy tube device that allowed precise placement of the tube through a tracheostomy stoma and through the area of the graft. When, after several days, it is determined that adequate ventilation can be achieved with the tube, a tracheostomy tube (Shiley Corp., Irvine, CA) is manufactured to conform to the size, length, and configuration of the endotracheal tube. The patients are eventually discharged with this custom-made long tracheostomy tube in place. Periodic reassessment of the graft by outpatient bronchoscopy is performed. When sufficient healing has occurred, as judged by the appearance, lumen size, and rigidity of the trachea and graft, a shorter tracheostomy tube of equivalent diameter is inserted and removed later when appropriate.

## Result

All five of the patients in this series survived the operative procedure. Three of five patients are long-term survivors, having been discharged from the hospital, and the tracheostomy tube, if used, eventually removed. Patients 4 and 5 died before they could be discharged. Patient 4 died 5 months after extensive cartilage graft reconstruction and had been weaned from the ventilator. Viral pneumonia developed in this patient, with subsequent copious tracheal secretions. These secretions completely occluded his airway on several occasions, resulting in severe hypoxic episodes. Hypoxic encephalopathy and a seizure disorder developed, rapidly progressing to coma. He died 10 days later of encephalopathy. At autopsy his cartilage graft was found to be well healed, with adequate lumen size, but he had evidence of severe bronchopneumonia. Patient 5 died 8 weeks after cartilage graft reconstruction. Refractory *Pseudomonas* tracheitis developed and significant tracheostomy hemorrhage occurred in this child after a tracheostomy tube change, which stopped spontaneously. Tracheoaortic fistula was suspected, but before further work-up could be accomplished, another hemorrhage intervened that could not be controlled by tamponade. The patient underwent emergency thoracotomy and was placed on extracorporeal circulation but the aortotracheal fistula could not be repaired and the patient died. Autopsy showed that the infected graft had eroded into the aorta.

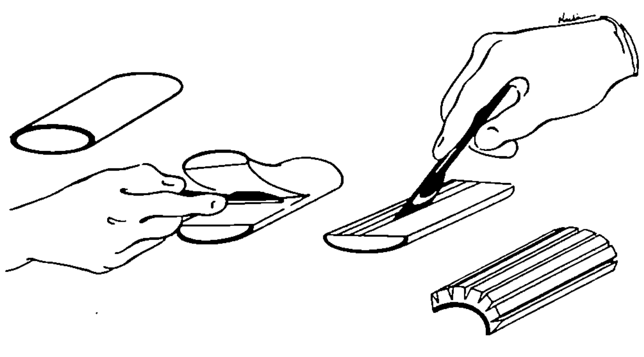

FIG. 6. Technique for preparing rib cartilage graft. The cartilage is harvested with the perichondrium intact, then is cut as shown. Longitudinal partial-thickness slits allow the graft to assume a dome shape, with perichondrium to the inside of the trachea.

The other three patients are well 3 to 6 years after operation. All are without tracheostomy tubes and have shown normal tracheal growth at bronchoscopy.

## Discussion

The survival of patients with congenital tracheal stenosis has improved in recent years, due to improvements in anesthesia techniques, operative management, and intensive care. However the outlook of the child with critical tracheal/bronchial stenosis associated with unilateral pulmonary aplasia, a known association, has continued to be extremely poor. Most of the reported patients have undergone desperate attempts at tracheal reconstruction, using a variety of techniques, with few successes reported.[3-5] However the present report documents that survival can be achieved in these infants with tracheal anomalies that previously were thought to be lethal. The important points in the management of these infants seem to be individualized therapy, based on as thorough a work-up as can be safely performed before operation, careful cooperation between surgeon and anesthesiologist, and flexibility both during and after operation. Most of these repairs can be performed without cardiopulmonary bypass by simply having the anesthesiologist advance the endotracheal tube past the point of obstruction, if possible, after resection or opening the trachea anteriorly. This allows adequate ventilation while the repair is completed. An occasional patient, such as patient 4 in this series, will have generalized narrowing into the hilum. In these instances, the immediate use of extracorporeal membrane oxygenation, followed several days later by work-up and repair of the tracheal stenosis, allows at least an attempt at repair that would not have been possible without extracorporeal circulation. Although the child eventually died of neurologic complication, his graft healed well and he had no tracheal narrowing at the time of his death.

In patients with short-segment stenosis, the ideal therapy is excision of the trachea, with end-to-end anastomosis. This was performed successfully in one of our patients (patient 1), and was used by Harrison et al.[4] Infants with more extensive tracheal narrowing require complex reconstruction. Successful use of rib cartilage grafts reported by Kimura[1] prompted us to use this technique in four of our five patients, with excellent healing in three patients. Multiple bronchoscopies at postoperative intervals in surviving patients, and autopsy in patient 3 have shown excellent healing and growth of these cartilage grafts. This confirms Kimura's observation.[1]

The long-term follow-up of the three surviving infants has shown normal respiratory function and, equally importantly, normal neurologic outcome and development. This latter observation is particularly important because of the multiple episodes of hypoxia, hypercarbia, and acidosis these infants suffered before and during repair. This re-emphasizes the capacity that infants have for recovery from critical illness in the newborn period and demonstrates that prolonged hospitalization, with multiple clinical 'set-backs,' can still result in an excellent outcome.

Nearly successful result with extracorporeal membrane oxygenation used before attempted repair of extensive tracheal stenosis warrants further investigation into the role of this new invasive life-support technique in the management of these critically ill infants.

## References

1. Kimura K, Mukohara N, Tsugawa C, et al. Tracheoplasty for congenital stenosis of the entire trachea. J Pediatr Surg 1982; 17: 869–871.
2. Weber TR, Pennington DG, Connors R, et al. Extracorporeal membrane oxygenation for newborn respiratory failure. Ann Thorac Surg 1986; 42:529–535.
3. Nelson CS, McMillan KR, Bharucha PK. Tracheal stenosis, pulmonary agenesis, and patent ductus arteriosus. Thorax 1967; 22: 7–12.
4. Harrison MR, Heldt GP, Brasch RC, et al. Resection of distal tracheal stenosis in a baby with agenesis of the lung. J Pediatr Surg 1980; 15:938–943.
5. Lobe TE, Hayden CK, Nicolas D, Richardson CJ. Successful management of congenital tracheal stenosis in infancy. J. Pediatr Surg 1987; 22:1137–1142.

# Synthesis of Type I Collagen in Healing Wounds in Humans

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**To quantify wound healing in surgical patients, samples of wound fluid were collected through a silicone rubber tube for 7 postoperative days and their concentrations of the carboxyterminal propeptide of type I procollagen (PICP) and the aminoterminal propeptide of type III procollagen (PIIINP) were measured with specific radioimmunoassays. The mean concentration of PICP in wound fluid on day 1 was 207 ± 92 (SD) $\mu$g/L, and on day 2 908 ± 469 $\mu$g/L ($p < 0.001$, signed rank test). On day 7, the mean concentration reached was 380 times higher than that of day 1 (79,330 ± 54,151 $\mu$g/L). Only one peak of PICP antigenicity, corresponding to the intact propeptide as set free during synthesis of type I procollagen, was detected on Sephacryl S-300 gel filtration analysis of wound fluid samples. The mean concentration of PIIINP was 70 ± 61 $\mu$g/L on day 1, 86 ± 88 $\mu$g/L on day 2, and 180 ± 129 $\mu$g/L on day 3 ($p < 0.001$ when compared with day 1). Finally on day 7, a 250-fold concentration (17,812 ± 9839 $\mu$g/L), compared with day 1, was reached. Methods described in the present paper allow separate and repetitive quantification of the synthesis of both type I and type III procollagen during human wound healing.**

THE STRENGTH OF a healing wound ultimately is based on collagen.[1] Proliferation of fibroblasts and synthesis of new collagen predominate in the proliferative phase of the healing process. Both type I and type III collagens are found in the granulation tissue, the proportion of the latter being higher than in the surrounding dermis.[2] A sequential appearance of type I and III collagens has been suggested on the basis of immunohistochemical studies.[3,4]

The fiber-forming collagens (types I, II, III, and V) are synthesized as procollagens, which contain additional propeptide extensions at both ends.[5] These are cleaved off *en bloc* when collagen molecules are deposited in the tissue. The complete removal of the carboxyterminal propeptides is necessary for proper fiber formation, where as not all the aminoterminal propeptides, especially those of type III procollagen, are cleaved off. Such type III pN collagen molecules are found on the surface of the fibers, where they probably prevent further growth of the fibril.[6] Previously we showed[7] that type III procollagen synthesis can be measured directly in a healing human wound *in situ* applying a specific radioimmunoassay for the aminoterminal propeptide of type III procollagen (PIIINP). The PIIINP antigen in wound fluid was derived mainly from new formation of type III collagen.

Type I collagen is the most abundant protein component of the granulation tissue.[8] Because of its complete removal and stoichiometric release during the formation of fibers, the carboxyterminal propeptide of type I procollagen (PICP) in wound fluid is theoretically a good indicator of the synthesis of this collagen type. We recently developed a radioimmunoassay for human PICP.[9] In the present study, the PICP concentration was measured in human wound fluid for up to 7 days after wounding. The size distribution of the antigen also was studied, as was the possible sequential appearance of collagen types I and III.

## Materials and Methods

### *Patients*

Twenty consecutive patients, 4 men and 16 women, were studied (mean age, 65 years; range, 44 to 82 years). They were electively operated on at Oulu University Central Hospital for colorectal cancer. Standard operative methods (resection of the colon or rectum in 14 patients,

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abdominoperineal excision of the rectum in 5, and exploratory laparotomy in 1) were used. For wound infection prophylaxis, single doses of doxycycline (400 mg) and metronidazole (1 g) were given intravenously at the induction of anesthesia. The tumor staging[10] was as follows: stage A, 5 patients; stage B, 5 patients; stage C, 6 patients; and stage D, 4 patients. Ten of the patients had a previous operation through the same incision 4 to 20 years earlier. Two of the patients had diabetes, one being treated with glibenclamid and the other with a sugar-free diet only. None of the patients used steroid medication. The predefined exclusion criteria included a recent (less than 1 year) operation through the same incision and the patient's unwillingness to participate in the study. The study was approved of by the Ethical Committee of the Medical Faculty of the University of Oulu and was carried out according to the provisions of the Declaration of Helsinki.

### *Collection of Wound Fluid*

For collecting wound fluid, two 15-cm Silastic® silicone rubber tubings (Dow Corning [Midland, MI] medical grade tubing no. 602-235, external diameter 2 mm) were left subcutaneously in the wound at the end of the operation, as previously described.[7] Samples of wound fluid were then drawn daily for 7 days by puncturing the tubing. The volume of the fluid (maximum amount drawn, 1 mL) was measured and the appearance determined visually as bloody, semiserous, or serous. All the samples were stored at −20 C until analyzed. Before analysis all the wound fluid samples were diluted 1:10 with phosphate-buffered saline, pH 7.2, containing 0.04% of Tween 20 (ICI Americas, Wilmington, DE). Further dilutions, when necessary, also were made in this buffer.

The tubes of one patient were detached before collection of the fourth day sample and her data were excluded. Some samples were inadvertently not taken or had other technical problems (*e.g.*, too high a dilution of two samples). Thus the total number of wound fluid samples examined was 18, 18, 16, 15, 16, 15, and 18 for days 1 to 7, respectively. No wound healing complications were seen. A blood sample also was taken from all the patients before operation to determine serum PICP and PIIINP concentrations.

### *Radioimmunoassay for Analyzing Wound Fluid PICP*

A recently developed radioimmunoassay[9] was used for analyzing the concentration of the carboxyterminal PICP. The assay was established by isolating type I procollagen from the medium of primary cultures of human skin fibroblasts and by digesting it with highly purified bacterial collagenase to liberate PICP. The released PICP finally was purified with lectin affinity, gel filtration, and anion exchange chromatographies. The polyclonal antiserum against the propeptide was raised in rabbits. The radioimmunoassay procedure was briefly as follows: 0.1 mL of an antiserum dilution capable of binding about 50% of the labeled antigen was incubated for 2 hours at +37 C with 0.1 mL of unlabeled standard antigen or unknown sample before adding 0.1 mL of $^{125}$I-labeled PICP. After a further incubation of 1 hour at +37 C, the free and bound antigens were separated by overnight precipitation at +4 C with a goat antiserum (second antibody) against rabbit IgG. The precipitate was collected by centrifugation for 30 minutes at +4 C, dissolved in 1 mL of phosphate-buffered saline, and recentrifuged. The radioactivity in the precipitate then was counted using an LKB-Wallac Multigamma gamma counter (Turku, Finland). Dilutions of 1:40 to 1:160 could be used for the first- to third-day samples, but up to 1:10,000 (most often 1:4000) dilutions of the seventh-day samples were required for reaching the measuring range of the assay. All the samples of each patient were determined in the same run. The intra-assay coefficient of variation was 5%.

### *Radioimmunoassay for Analyzing Wound Fluid PIIINP*

The concentration of the aminoterminal propeptide of type III procollagen (PIIINP) was analyzed with a sequential modification of a radioimmunoassay[11] based on the human antigen (Farmos Diagnostica, Oulunsalo, Finland). The antiserum and the assay conditions have been selected so that the authentic propeptide and another, somewhat larger, PIIINP related antigen are detected, but the assay is not sensitive to the smaller degradation products of the propeptide. With this method the standards and samples of biologic fluids give parallel inhibition curves. We previously demonstrated that this assay reflects the synthesis of type III procollagen in human wounds.[7,12] The actual laboratory procedure was comparable to that of the PICP assay described above. The volumes used were 0.1 mL for antiserum, 0.1 mL for standard, and 0.2 mL for samples. Dilutions of 1:20 to 1:100 were suitable for the first- to third-day samples, but up to 1:8000 (usually 1:4000) dilutions of the seventh-day samples were necessary. The intra-assay coefficient of variation was 4%.

### *Gel Filtration Analysis of Wound Fluid PICP*

Gel filtration of 100-μL samples of the first-day and fourth-day wound fluid and a 50-μL sample of the seventh-day wound fluid was carried out on a column (1.5 × 110 cm) of Sephacryl S-300 (Pharmacia, Uppsala, Sweden) equilibrated in 0.2 mol/L (molar) $(NH_4)HCO_3$, pH 7.9. Seventy fractions of 2.5 mL were collected from each sample. Aliquots (400, 100, and 25 μL) of each fraction of the first-, fourth-, and seventh-day wound fluid, respectively, then were analyzed with the PICP radioimmunoassay using the conditions described above.

### *Clinical Variables*

The clinical variables recorded included the type and the interval from any previous operation and specifically the operations through the same incision, the staging of the tumor, operative blood loss, duration of the operation, postoperative complications, the hematocrit value, and the hemoglobin and serum albumin concentrations.

### *Statistical Analysis*

The statistical analyses were done with Statgraphics® Software (STSC, Inc., Rockville, MD). The results of wound fluid PICP and PIIINP concentrations are given as means with standard deviations (SD) or with standard errors as indicated in the text and the figures. Wilcoxon signed rank test for paired observations was used when comparing later concentrations of PICP and PIIINP with those of day 1, $p < 0.05$, evaluated from standard tables for small samples, was considered as statistically significant. The Spearman rank correlation coefficient was calculated when clinical and sampling variables were compared to the concentrations of PICP and PIIINP. It also was used for comparisons between the PICP and PIIINP concentrations on the different postoperative days.

## Results

### *PICP and PIIINP in Wound Fluid*

The mean concentration of PICP in wound fluid on day 1 was 207 ± 92 (SD) µg/L. Already on day 2 it was 908 ± 469 µg/L ($t = 0$, $z = 3.8$, $p < 0.001$), and 3246 ± 2858 µg/L on day 3 (Fig. 1). On day 7 the mean concentration had reached a level 380 times that of day 1 (79,330 ± 54,151 µg/L). The individual differences were great, *e.g.*, at day 7 the range was from 19,750 to 198,813 µg/L. The mean PIIINP concentrations (Fig. 2) changed more slowly, no increase being found between the first 2 days (70 ± 61 µ g/L on day 1 and 86 ± 88 µg/L on day 2; $t = 64$, $z = 1.2$, $p = 0.2$), but on day 3 the concentration was increased to 180 ± 129 µg/L ($t = 0$, $z = 3.48$, $p < 0.001$). Finally on day 7, the PIIINP concentration in the wound was 250 times that of day 1 (17,812 ± 9839 µg/L).

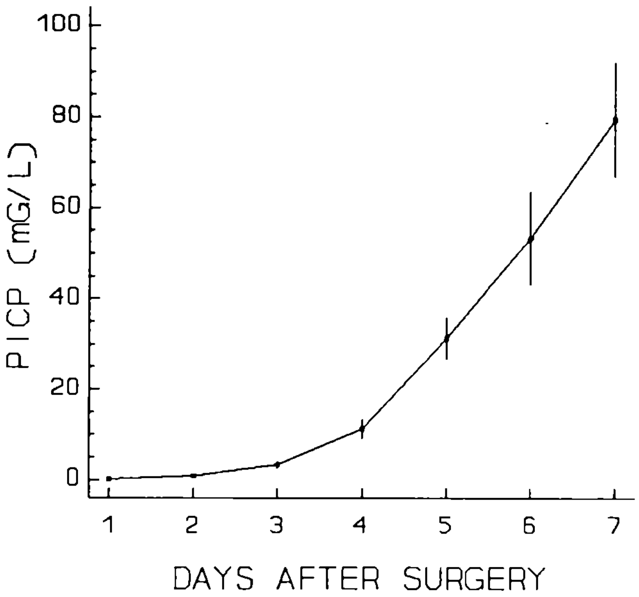

FIG. 1. Effect of time on the concentration of the carboxyterminal propeptide of type I procollagen (PICP) in wound fluid of patients operated on for colorectal cancer (mean, SE).

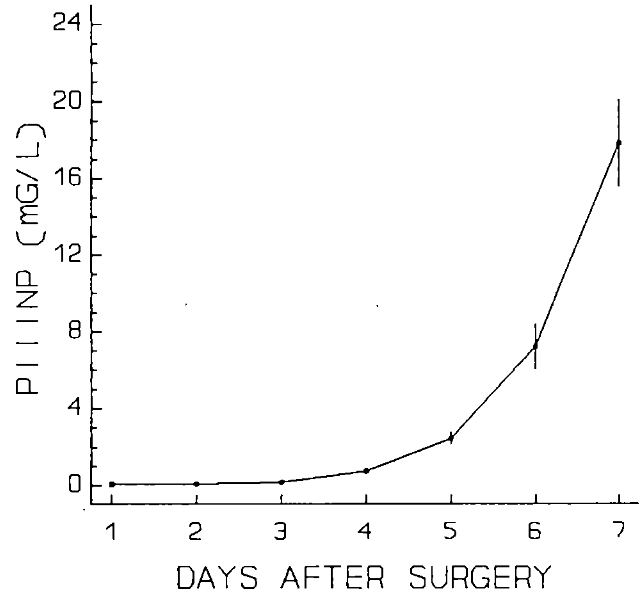

FIG. 2. Effect of time on the concentration of the aminoterminal propeptide of type III procollagen (PIIINP) in wound fluid of patients operated on for colorectal cancer (mean, SE).

The mean preoperative serum concentration of PICP was 82 ± 35 (SD) µg/L and that of PIIINP 3.5 ± 1.9 µg/L. Thus the mean wound fluid PICP concentration on day 1 was about twice as high as in preoperative serum. However at the same time the mean wound fluid PIIINP concentration was 20 times higher than that in serum.

### *Gel Filtration Analysis of Wound Fluid PICP*

Gel filtration on a column of Sephacryl S-300 was used to study the size of the PICP antigen in the wound. Only one peak of PICP antigenicity was detected on days 4 and 7 (Fig. 3). The elution position of this peak was equal to that of the authentic, $^{125}$I-labeled, human PICP, which was run separately on the column. The PICP eluted between IgG and albumin corresponding to a molecular weight of a globular protein of about 100,000. No larger molecules, corresponding to uncleared type I procollagen, were seen at any time, indicating an efficient processing

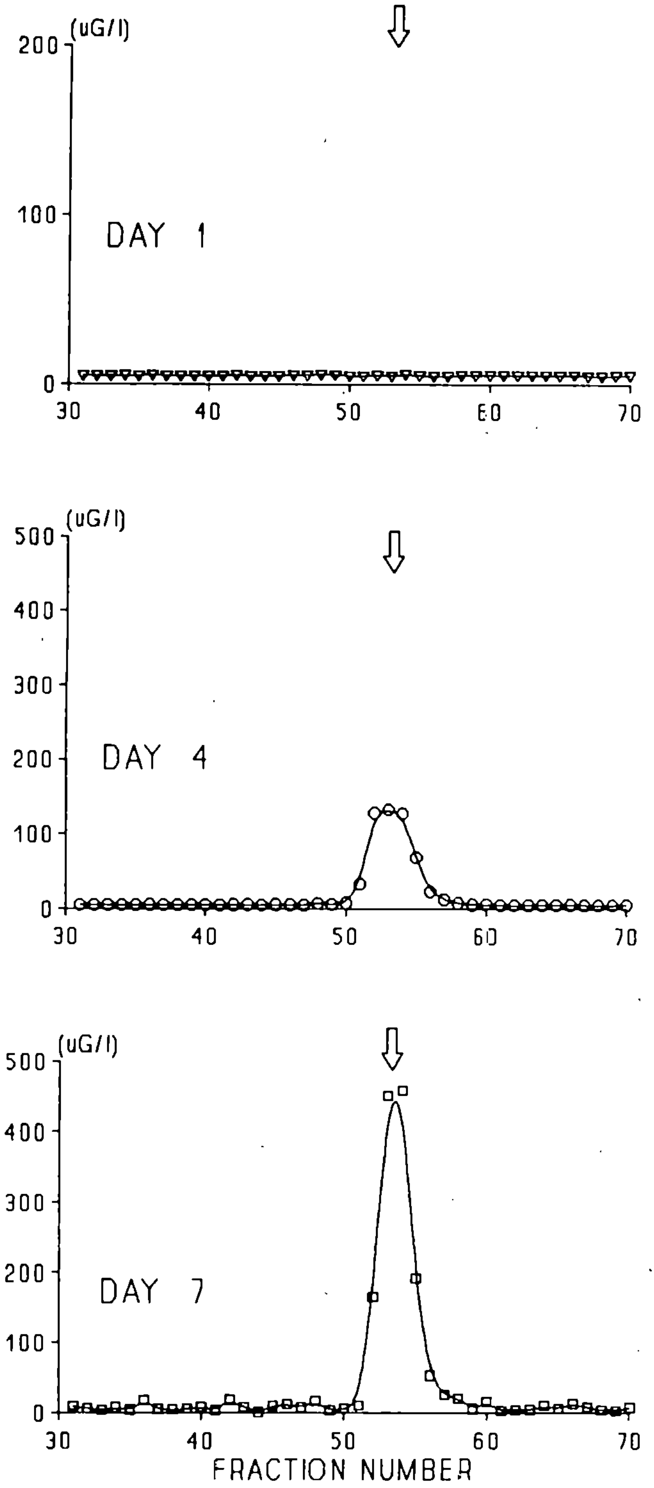

FIG. 3. Location of the PICP antigen in the gel filtration fractions of wound fluid on postoperative days 1, 4, and 7. The concentration of PICP in first-day wound fluid was unmeasurable in the diluted sample. The arrow indicates the elution position of the isolated and labeled human PICP.

of procollagen in the wound. On day 1, the concentration of PICP in the gel filtration fractions was too low to be measured.

### *Relation Between the Collagen Types I and III*

During early wound healing there was no correlation between the wound fluid PICP and PIIINP concentrations (Table 1), but after day 3 high correlations were seen.

The proportion of type III procollagen of the sum of type I and type III procollagens in the wound also was assessed. The calculations are based on the known molecular weights of the PICP ($M_r$ 100,000), PIIINP ($M_r$ 42,000), and type I and III procollagens ($M_r$ 450,000). The results are given as a box-and-whiskers plot in Figure 4. The median for the proportion of type III procollagen was initially about 40%, decreasing to 14% during days 3 and 4, and then increasing up to 37% at day 7.

### *Effect of Sampling and Clinical Variables*

Sixteen (84%) of the first-day, 13 (72%) of the second-day, and 6 (50%) of the third-day samples were bloody. On the seventh day, 4 samples were bloody, 5 were semiserous, and 10 were serous. The quality of the sample had no effect on either the PICP or the PIIINP concentrations on any postoperative day. The mean volumes of fluid obtained on the 7 postoperative days were 620 $\mu$L (range, 100 to 1000 $\mu$L), 495 $\mu$L (range, 100 to 1000 $\mu$L), 286 $\mu$L (range, 100 to 1000 $\mu$L), 342 $\mu$L (range, 100 to 1000 $\mu$L), 421 $\mu$L (range, 100 to 1000 $\mu$L), 431 $\mu$L (range, 80 to 1000 $\mu$L), and 388 $\mu$L (range, 80 to 1000 $\mu$L), respectively. The amount of wound fluid drawn had no effect on the concentrations measured.

Ten patients had a previous incision partly or totally overlapping with the present one with the minimum interval of 4 years and the mean interval of 16 years between the operations. There was no difference in the mean wound fluid concentrations of PICP or PIIINP on any postoperative day between the previously operated and nonoperated patients. Previous surgery elsewhere in the body had no effect on the wound healing parameters. The same was true for the stage of the tumor, operative blood loss, duration of the operation, postoperative complications, hematocrit, hemoglobin, and serum albumin. The wound fluid concentrations of both PICP and PIIINP of the diabetic patient treated with glibenclamid were less

TABLE 1. *Spearman Rank Correlation Coefficients Between the Wound Fluid PICP and PIIINP Concentrations on Postoperative Days 1 through 7*

| Day | r | n | p |
|---|---|---|---|
| 1 | 0.32 | 18 | 0.18 |
| 2 | 0.13 | 18 | 0.59 |
| 3 | 0.50 | 16 | 0.05 |
| 4 | 0.89 | 15 | 0.0005 |
| 5 | 0.85 | 16 | 0.001 |
| 6 | 0.82 | 15 | 0.002 |
| 7 | 0.69 | 18 | 0.004 |

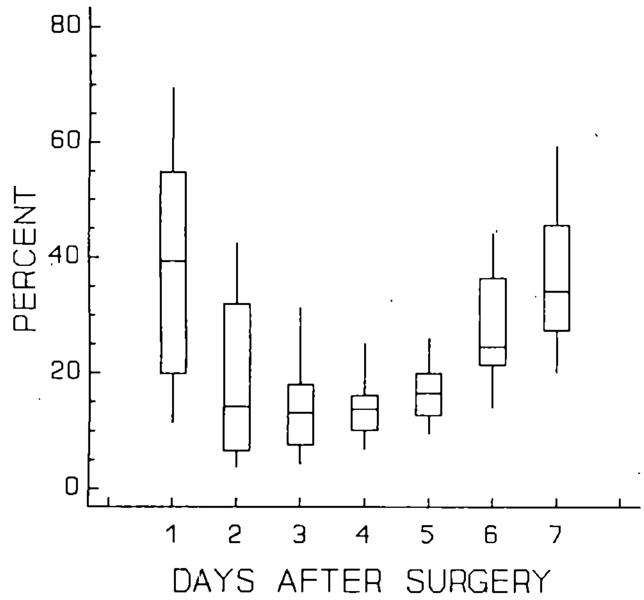

FIG. 4. Box-and-whiskers plot with median, range, and interquartile range for the proportion of type III procollagen from the sum of type I and type III procollagen to be synthesized in the wound. The calculation is based on the molecular weights of PICP, PIIINP, and respective procollagens and on the fact that there is a stoichiometric relation between a certain propeptide and its respective procollagen molecule. On days 1 and 2, PIIINP-related antigens, possibly derived from the degradation of tissue type III pN-collagen, may lead to an overestimation of the proportion (see Discussion).

than the lower quartile of the whole group, but three patients had still lower levels, with no apparent reason.

## Discussion

The characteristics and biochemical basis of the tensile strength of a healing wound have been studied extensively.[1,13] The cellular events involved and the chemical composition of granulation tissue are well known. In our previous study, we quantified type III procollagen-related antigens for up to 5 days in wound fluid with a specific radioimmunoassay.[7] In the present study, almost identical results concerning type III procollagen were achieved, indicating good reproducibility of the method. Wound fluid sampling was now extended to day 7, and measurement of type I procollagen synthesis was made possible by a new specific radioimmunoassay for its carboxyterminal propeptide. Here this method was applied to human wound healing studies for the first time.[14,9]

The assay for the carboxyterminal propeptide of type I procollagen seems to be a useful indicator of human wound healing. Because this propeptide, without exception, is set free during the synthesis of new type I collagen, the concentration of the PICP antigen can be considered as a direct measure of collagen type I synthesis. The result of the gel filtration analysis with only one peak of PICP antigenicity supports this conclusion. Furthermore, because there is no cross-reaction between PIIINP and PICP, separate and repetitive quantification of the synthesis of two important components of a healing wound is possible. PICP is also present in serum, where most of it is probably derived from the continuous turnover of skeletal collagen. In wound fluid the PICP concentration was initially about twice as high as that in serum and later up to 1000 times higher than that in serum. For PIIINP the difference between the initial concentrations in wound fluid and serum was far greater. This is not necessarily a consequence of a very early initiation of type III collagen synthesis in the wound, but may be partly or completely due to the fact that in serum the PIIINP antigen is further degraded to smaller peptides that are not measured with the assay modification used in this study.[7,11,12]

Analyses of the collagen types I and/or III in wounds or in experimentally induced granulation tissue were first reported 15 years ago.[2, 15–17] In granulation tissue, higher concentrations of both collagen types are found than in the surrounding dermis, but there has been a large variation with respect to the timing and the proportions of collagen types I and III, probably due to differences in the methods used.[2, 15–17,3,4,18,19] A relatively constant finding has been an increased proportion of type III collagen production in early granulation tissue, according to one study up to 62% of the sum of the types I and III.[20] A similar phenomenon can be reproduced *in vitro*: mononuclear leukocytes stimulate fibroblastic cells to increase their type III collagen production from 6% to 16%.[21]

In the present study, the smallest proportion of type III procollagen synthesis was 14% of the sum of type I and III collagen synthesis, with higher values during the first and last days of the collection. The increasing proportion of type III procollagen (Fig. 4) toward the end of the study period could be interpreted as an earlier response of type III collagen synthesis, as in other studies.[3,4] As reported in our previous papers,[7,12] up to 95% of the PIIINP antigen in the wound is derived from the authentic propeptide as set free during the synthesis of type III collagen. Day 7 was studied in greater detail. Thus the calculations based on the relative amounts of PICP and PIIINP probably give good estimates for the proportional rates of synthesis of the procollagen types, possibly excluding days 1 to 3 (see below).

It has been suggested that the synthesis of type III procollagen begins as early as 10 hours after wounding.[18] This could be a partial explanation for the large proportion of type III procollagen detected during days 1 and 2 in our study, but the transient decrease in its proportion later on days 3 and 4 would be unexpected. However, another explanation would be that PIIINP-related antigens derived from the breakdown of tissue type III pN collagen would be responsible for the initial PIIINP concentrations.[12] Also the initial lack of correlation between the PICP and PIIINP concentrations (Table 1) suggests that there are additional independent factor(s) behind the higher proportion of the type III procollagen-related antigens. Even during the highest net synthesis, protein turnover has its two sides, synthesis and degradation.[22] Metalloproteinases that are capable of degrading collagen are active during the inflammatory phase of healing.[22–24]

Enhancement of the healing process is an area of intensive research. It is to be expected that methods for assessing collagen synthesis rates, such as those used in this paper, will be useful for measuring wound healing responses. However, from the point of view of attaining a better hold of the sutures, it is probably as important to prevent lysis of pre-existing collagen.[23,24] The degradative processes may also be important in chronic ulcers. Thus there is also a need to assess collagenolysis in the wound.

## Acknowledgments

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## References

1. Forrest L. Current concepts in soft connective tissue wound healing. Br J Surg 1983; 70:133–140.
2. Barnes MJ, Morton LF, Bennett RC, et al. Presence of type III collagen in guinea pig dermal scar. Biochem J 1976; 157:263–266.
3. Gay S, Viljanto J, Raekallio J, Penttinen R. Collagen types in early phases of wound healing in children. Acta Chir Scand 1978; 144: 205–211.
4. Kurkinen M, Vaheri A, Roberts PJ, Stenman S. Sequential appearance of fibronectin and collagen in experimental granulation tissue. Lab Invest 1980; 43:47–51.
5. Prockop DJ, Kivirikko KI, Tuderman L, Guzman NA. The biosynthesis of collagen and its disorders. Review. N Engl J Med 1979; 301:13–23, 77–85.
6. Hulmes DJS. A possible mechanism for the regulation of collagen fibril diameter in vivo. Collagen Related Research 1983; 3:317–321.
7. Haukipuro H, Risteli L, Kairaluoma MI, Risteli J. Aminoterminal propeptide of type III procollagen in healing wound in humans. Ann Surg 1987; 206:752–756.
8. Kanzler MH, Gorsulowsky DC, Swanson NA. Basic mechanisms in the healing cutaneous wound. J Dermatol Surg Oncol 1986; 12:1156–1164.
9. Melkko J, Niemi S, Risteli L, Risteli J. Radioimunoassay for the carboxyterminal propeptide of human type I procollagen. Clin Chem 1990, 36:1328–1332.
10. Davis NC, Evans EB, Cohen JR, Theile DE. Staging of colorectal cancer: the Australian clinico-pathological staging (ACPS) system compared with Dukes' system. Dis Colon Rectum 1984; 27:707–713.
11. Risteli J, Niemi S, Trivedi P, et al. Rapid equilibrium radioimmunoassay for the aminoterminal propeptide of human type III collagen. Clin Chem 1988; 34:715–718.
12. Haukipuro K, Risteli L, Kairaluoma MI, Risteli J. Aminoterminal propeptide of type III procollagen in serum during wound healing in humans. Surgery 1990;170:381–388.
13. Clark RAF. Cutaneous tissue repair: basic biologic considerations. I. Am Acad Dermatol 1985; 13:701–725.
14. Taubman MB, Goldberg B, Sherr CJ. Radioimmunoassay for human procollagen. Science 1974; 186:1115–1117.
15. Shuttleworth CA, Forrest L. Pepsin-solubilized collagens of guinea pig dermis and dermal scar. Biochim Biophys Acta 1974; 365: 454–457.
16. Bailey AJ, Bazin S, Sims TJ, et al. Characterization of the collagen of human hypertrophic and normal scars. Biochim Biophys Acta 1975; 405:412–421.
17. Bailey AJ, Sims TJ, Le Lous M, Bazin S. Collagen polymorphism in experimental granulation tissue. Biochem Biophys Res Comm 1975; 66:1160–1165.
18. Clore JN, Cohen IK, Diegelmann RF. Quantitation of collagen types I and III during wound healing in rat skin. Proc Soc Exp Biol Med 1979; 161:337–340.
19. Cohen IK, Moore CD, Diegelmann RF. Onset and localisation of collagen synthesis during wound healing in open rat skin wounds. Proc Soc Exp Biol Med 1979; 160:458–462.
20. Hørslev-Petersen K, Kim KY, Pedersen LR, et al. Serum aminoterminal type III procollagen peptide. Relation to biosynthesis of collagen type III in experimentally induced granulation tissue in rats. APMIS 1988; 96:793–804.
21. Hibbs MS, Postletwhaite AE, Mainardi CL, et al. Alterations in collagen production in mixed mononuclear leucocyte-fibroblast cultures. J Exp Med 1983; 157:47–59.
22. Laurent GJ. Dynamic state of collagen: pathways of collagen degradation in vivo and their possible role in regulation of collagen mass. Am J Physiol 1987; 252 (Cell Physiol 21):C1-C9.
23. Högström H, Haglund U. Postoperative decrease in suture holding capacity in laparotomy wounds and anastomoses. Acta Chir Scand 1985; 151:533–535.
24. Högström H, Haglund U. Early decrease in suture line breaking strength. The effect of proposed collagenase inhibition. Res Exp Med 1985; 185:451–455.

# Role of Granulocyte Elastase in Tissue Injury in Patients with Septic Shock Complicated by Multiple-organ Failure

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**To better understand the role of granulocyte elastase (GE) in mediating tissue injury during sepsis, GE levels were measured in plasma and bronchoalveolar lavage fluid (BALF) in patients with septic shock (n = 16) and hemorrhagic shock (n = 30). Granulocyte elastase levels were compared to levels of α1-protease inhibitor (α1-PI). Results show that although plasma GE-α1-PI complex was initially elevated in patients with hemorrhagic and septic shock, elevations in plasma GE-α1-PI complex (831 ± 241 μg/L) persisted in septic shock patients. α1-Protease inhibitor levels in serum were increased, resulting in an inhibition of serum GE activity. Granulocyte elastase activity in BALF, however, was significantly higher in those patients with septic, as compared to hemorrhagic shock (31.4 ± 25.8 *versus* 3.7 ± 4.0 U/L, respectively). In addition GE levels were compared to other parameters, including respiratory index, blood neutrophil count, and plasma levels of endotoxin, fibronectin, and coagulation factor XIII. Significant correlations were observed between GE-α1-PI and increased endotoxin concentration and decreased fibronectin and coagulation factor XIII levels. Significant correlation was found also between GE activity in BALF and respiratory index. These findings suggest that severe tissue damage occurred in patients with septic shock complicated by multiple-organ failure. Although GE activity appeared to be adequately inhibited by α1-PI in blood, increased GE activity in local tissues, such as lung alveoli, may be responsible for significant local tissue injury during septic shock.**

MULTIPLE-ORGAN FAILURE (MOF) sometimes occurs in patients suffering severe trauma or burns complicated by uncontrolled infection.[1] However the pathophysiology of MOF is not well understood. Tissue hypoxia and such chemical mediators as oxygen radicals and proteases may be involved in the development of MOF.[2,3]

Granulocyte elastase (GE), a key participant in the inflammatory response, functions in the mediation of host responses to inflammation. When neutrophils are stimulated by one of any number of factors, including endotoxin, opsonized immunocomplexes, or complement,[4] GE is released. Therefore it plays a significant role in the degradation of foreign matter.[5] Granulocyte elastase is a potent proteolytic agent, however, and is capable of lysing a wide variety of normal tissue substrates, including clotting and fibrinolytic factors, fibronectin, and tissue components.[6]

Granulocyte elastase also is believed to be involved in the pathogenesis of certain clinical disorders, including pulmonary emphysema due to congenital α1-protease inhibitor (α1-PI) deficiency[7] or cigarette smoking.[8] Recent studies using an enzyme-linked immunosorbent assay (ELISA) found high plasma concentrations of GE-α1-PI complex in patients with adult respiratory distress syndrome, rheumatoid arthritis,[9] and some infectious diseases.[10] However the proteolytic activity of GE in blood has not been evaluated because the GE measured usually is complexed with α1-PI. Thus the role of GE in tissue injury has not been clarified fully.

A new method has been developed in our laboratory to measure GE activity in tissue fluids.[11] We use the chromogenic synthetic substrate L-pyroglutamyl-L-prolyl-L-valine-p-nitroanilide (L-Glu-Pro-Val-pNA), which is more sensitive and specific for GE than those previously reported.

In this study we measured serial changes in the plasma levels of GE-α1-PI complex in patients with septic shock complicated by MOF and patients with hemorrhagic shock, and compared these levels with several other parameters. In addition we measured GE hydrolytic activity and α1-PI activity in blood and bronchoalveolar lavage fluid (BALF) and evaluated the role of GE in tissue injury.

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## Patients and Methods

### *Patients*

Plasma levels of GE-$\alpha$1-PI complex were measured in 46 patients who were admitted to department from September 1986 to September 1988. These patients were divided into two groups. Group 1 consisted of 16 patients with septic shock complicated by MOF, and group 2 consisted of 30 patients with hemorrhagic shock secondary to severe injury. In group 1 (patients with septic shock) there were 6 trauma patients, 4 burn patients, and 6 patients with panperitonitis. Shock continued for more than 7 days and all patients in group 1 had associated multiple-organ failure. All of the patients in group 2 were admitted with hemorrhagic shock, and all recovered from shock within 24 hours of blood transfusion and/or surgery. The diagnosis of sepsis was based on the presence of two or more of the following criteria: (1) fever of more than 39 C for more than 3 days; (2) a leukocyte counts of more than 15,000/$\mu$L; (3) a positive limulus test for endotoxin; (4) a positive blood culture; and (5) culture of the same organisms from an intravenous catheter tip and the focus of infection. Septic shock in septic patients was diagnosed by the following criteria: systolic blood pressure of less than 90 mmHg, decreased urine output (less than 1 mL/kg/hr), and a cardiac index of more than 4.5 or less than 2.5 L/min/m$^2$. A diagnosis of hemorrhagic shock was made using previously reported criteria.[12]

### *Blood Samples*

In group 1 blood samples were obtained with the diagnosis of septic shock (day 0), and on days, 1, 2, 3, 5, and 7 thereafter. In group 2 samples were obtained on admission (in hemorrhagic shock) and at follow-up intervals identical to those in group 1. They were immediately separated and stored at −70 C until the time of assay.

### *Plasma GE-$\alpha$1-PI Complex*

Plasma levels of GE-$\alpha$1-PI complex were determined with an ELISA kit (E. Merck, Darmstadt, FRG). The values are reported as the concentration of complexed elastase inhibited by $\alpha$1-PI and not active.

### *GE Activity in Serum and BALF*

L-Glu-Pro-Val-pNA (Kabi Diagnostica, Stockholm, Sweden) was dissolved in dimethyl sulfoxide and diluted four times with distilled water. The final concentration of the substrate was 2 mmol/L (millimolar). Granulocyte elastase activity was assayed by a new method developed in our laboratory.[11] Two hundred microliters of buffer (0.1 mol/L [molar] TRIS, 0.96 mol/L NaCl, pH 8.3) was added to 200 $\mu$L of sample and the reaction was initiated by the addition of 200 $\mu$L of substrate solution containing L-Glu-Pro-Val-pNA at 37 C. After incubation for 3 hours, diazotization was performed to enhance sensitivity after the addition of 500 $\mu$L of each of the following: 0.04% (w/v) sodium nitrite in 0.48 mol/L (molar) HCl, 0.3% (w/v) ammonium sulfamate, and 0.07% (w/v) N-1-naphthylethylenediamine dihydrochloride. Absorbance was measured at 545 nm after diazotization.

Bronchoalveolar lavage fluid was obtained on day 7 after diagnosis of shock from 11 patients in group 1 and 12 in group 2, according to the method of Lee et al.[13] Twenty-five milliliters of sterile 0.9% NaCl was instilled through an endotracheal tube and aspirated by suction. The cells, debris, and mucus were removed by centrifugation at 3000 RPM for 10 minutes.

### *$\alpha$1-PI Activity and Concentration*

$\alpha$1-Protease inhibitor activity in serum and BALF was measured as follows. Fifty microliters of sample was diluted with 1000 $\mu$L of buffer (0.5 mol/L TRIS, pH 8.0) containing 0.15 mol/L methylamine hydrochloride. The latter was used to hamper the effect of $\alpha$2-macroglobulin. An excess of trypsin (20 $\mu$mol/L [micromolar], 2 mmol/L HCl, 10 mmol/L CaCl$_2$) was added to 50 $\mu$L of diluted sample. During the incubation that followed, trypsin was inhibited by $\alpha$1-PI in the sample. The remaining trypsin was measured with the use of the chromogenic substrate L-benzoylarginine p-nitroanilide. After incubation for 20 minutes, absorbance was measured at 410 nm. Serum $\alpha$1-PI concentration was measured by single radial immunodiffusion.

### *Other Parameters*

Several other parameters were measured at the same time intervals after the diagnosis of shock. The respiratory index was calculated by AaDO2/PaO2, where AaDO2 is the alveolar-arterial oxygen difference, and PaO2 is the

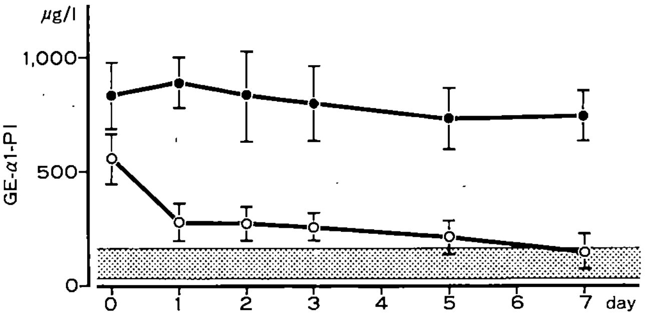

FIG. 1. Plasma levels of GE-$\alpha$1-PI ($\mu$g/L) in groups 1 (●) and 2 (O) measured at the diagnosis of shock (day 0), and days 1, 2, 3, 5, and 7 thereafter. Normal GE-$\alpha$1-PI values are represented by the shaded area.

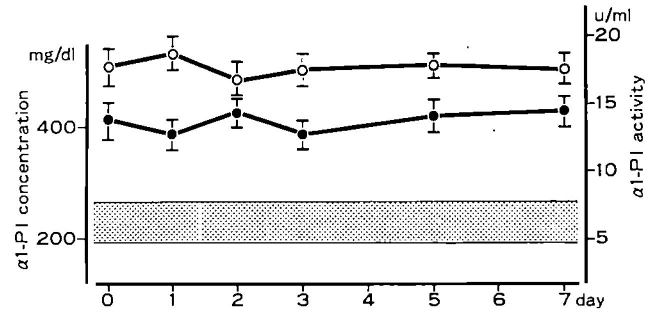

FIG. 2. Serial changes in $\alpha$1-PI concentration (●) and activitiy (O) after diagnosis of shock in group 1. Normal values are represented by the shaded area.

arterial partial pressure of oxygen.[14] Neutrophils were counted by an automated blood cell counter (CC-120, Sysmex, Towa Medical, Hyogo, Japan) and Wright-Giemsa staining. Endotoxin was measured in plasma by conventional chromogenic limulus testing[15] (Seikagaku Kogyo Co., Ltd., Tokyo, Japan). Plasma fibronectin was measured by single radial immunodiffusion and coagulation factor XIII was measured by the method of Bohn.[16]

### *Statistical Analysis*

All values are expressed as mean plus the standard deviation (SD). The data were analyzed by means of linear regression analysis and Student's t test. Differences were considered significant at the $p < 0.05$ level.

## Results

### *GE-αl-PI Complex in Blood*

Normal plasma GE-$\alpha$1-PI values ranged from 21 to 165 μg/L. Figure 1 shows the serial changes in GE-$\alpha$1-PI in both patient group. Levels in group 1 were elevated (831 ± 241 μg/L) at diagnosis of septic shock and remained high during the ensuing week. In group 2 GE-$\alpha$1-PI levels were high during hemorrhagic shock (574 ± 131 μg/L) but quickly returned to normal at recovery.

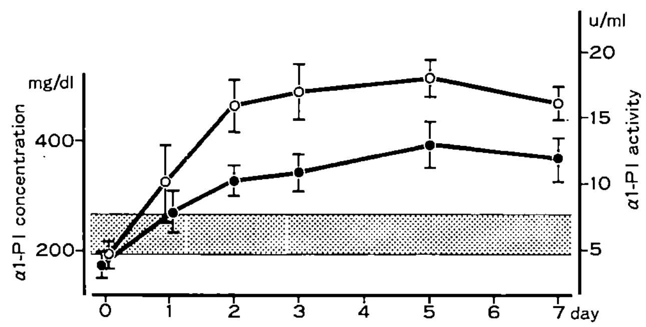

FIG. 3. Serial changes in $\alpha$1-PI concentration (●) and activity (O) after diagnosis of shock in group 2. Normal values are represented by the shaded area.

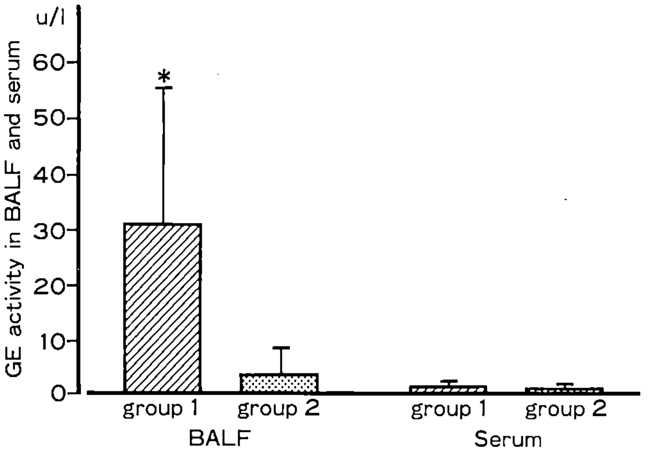

FIG. 4. Mean hydrolytic GE activity (U/L) in BALF and serum in the two groups on day 7 after diagnosis of shock. $^*p < 0.05$, group 1 *versus* group 2.

### *αl-PI Concentration and Activity in Blood*

Figure 2 illustrates the serial changes in $\alpha$1-PI concentration and activity in group 1. Both measures increased to twice the normal range at the time of the diagnosis of shock. In group 2 both measures decreased during shock but increased after recovery and thereafter persisted at twice the normal levels (Fig. 3).

### *GE and αl-PI Activity in BALF and Blood*

Figure 4 shows the hydrolytic GE activity in BALF and serum in the two groups on day 7. Mean GE activity in BALF was significantly higher in group 1 (31.4 ± 25.8 U/L) than in group 2 (3.7 ± 4.0 U/L). Granulocyte elastase activity in blood was barely detected in either group.

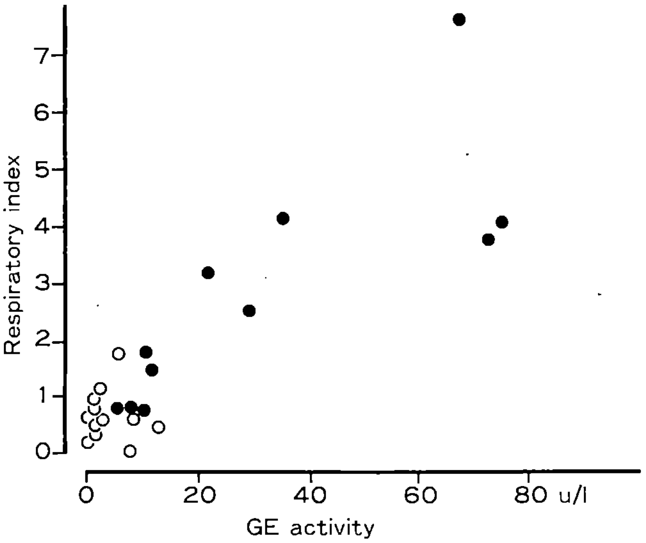

FIG. 5. Correlation between GE activity and the respiratory index. ●, group 1; O, group 2; $r = 0.86$, $p < 0.05$.

Granulocyte elastase activity in BALF and the respiratory index, as shown in Figure 5, were significantly and positively correlated ($r = 0.86$, $p < 0.05$). Figure 6 shows the α1-PI activity in BALF and serum on the seventh day following the diagnosis of shock. In both groups, α1-PI activity was lower in BALF than in serum.

### *Neutrophils, Endotoxin, Fibronectin, and Coagulation Factor XIII in Blood*

Table 1 summarizes the averaged data from days 3 and 7 for blood neutrophil counts, and plasma endotoxin, fibronectin, and coagulation factor XIII and their relationship to plasma GE-α1-PI levels. There was no significant difference in the number of neutrophils between the two groups and no relationship between the levels of GE-α1-PI and the neutrophil counts. However the ratio of GE-α1-PI to neutrophils was significantly higher in group 1, as was the mean endotoxin concentration in blood (33 ± 12 pg/mL). In group 2 the latter was within the normal range at 6.4 ± 6.3 pg/mL. In addition there was a significant correlation between the endotoxin and GE-α1-PI levels ($r = 0.68$, $p < 0.05$).

In group 1 the fibronectin level decreased to 16.7 ± 6.1 mg/dL, while fibronectin remained within the normal range (27.6 ± 6.6 mg/dL) in group 2. There was a significant negative correlation between fibronectin and GE-α1-PI ($r = -0.71$, $p < 0.05$).

In group 1 coagulation factor XIII decreased during shock to 34% ± 10.1%. In group 2 this factor decreased during shock but soon recovered to 46.4% ± 10.7%. There was a significant negative correlation between coagulation factor XIII and GE-α1-PI ($r = -0.81$, $p < 0.05$).

TABLE 1. *Relationships Between Plasma GE-α1-PI Concentration and Neutrophil Count, Endotoxin, Fibronectin, and Coagulation Factor XIII Levels*

| | Group 1 | Group 2 | GE-α1-PI |
|---|---|---|---|
| Neutrophil ($\times 10^3/\text{mm}^3$) | 9413 ± 5437 | 8057 ± 3553 | NS |
| Endotoxin (pg/mL) | 33.2 ± 12.2* | 6.4 ± 6.3 | $r = 0.68$, $p < 0.05$ |
| Fibronectin (mg/dL) | 16.7 ± 6.1* | 27.6 ± 6.6 | $r = -0.71$, $p < 0.05$ |
| Factor XIII (%) | 34.0 ± 10.1* | 46.4 ± 10.7 | $r = -0.81$, $p < 0.05$ |

* $p < 0.05$, group 1 *versus* group 2.

Values are expressed as the mean ± SD of blood samples obtained from all patients on days 3 and 7 after diagnosis of shock.

## Discussion

The results of this study demonstrate that plasma GE-α1-PI complex is elevated in patients with shock. In hemorrhagic shock due to severe injury (group 2), plasma GE-α1-PI increased during shock but returned to normal at recovery. In contrast a marked increase in plasma GE-α1-PI was observed in patients in septic shock complicated by MOF but GE activity was not measurable in the blood in either group. This indicates that GE activity was neutralized by α1-PI, an acute-phase reactant and potent inhibitor of GE.[17] In healthy individuals GE is regulated by their ample inhibitory capacity outside the cell. However neutrophils, when stimulated, release oxygen radicals that create a zone of oxidation around them, forming a microenvironment within which α1-PI is inactivated.[18]

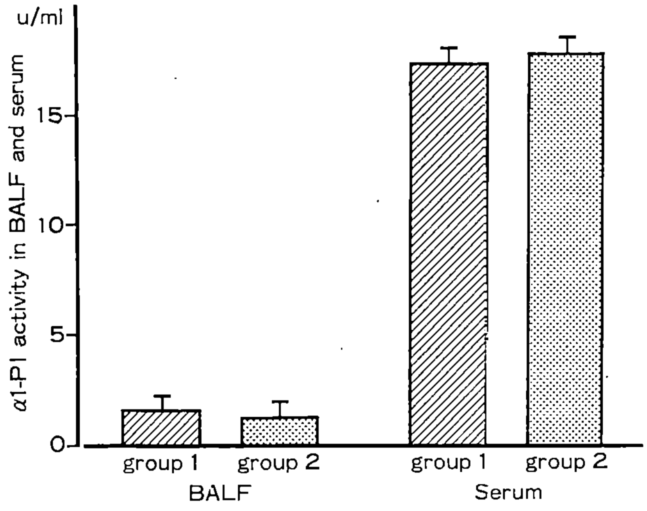

FIG. 6. Mean α1-PI activity (U/mL) in BALF and serum in the two groups on day 7 after diagnosis of shock.

In our earlier study we demonstrated that GE hydrolytic activity increases in the fluid of inflamed tissue, such as synovial fluid of patients with rheumatoid arthritis and blister fluid in burn patients.[11] In this study we found an increase in GE activity in BALF in patients with septic shock complicated by MOF. These patients had a high respiratory index, and the correlation between GE activity and the respiratory index was significant. In addition there was little α1-PI activity in BALF. These findings suggest that although GE activity is suppressed by increased α1-PI in blood, it may be significantly active in tissues in which it is not neutralized by a specific inhibitor. Respiratory failure occurs frequently in septic shock. It is thought that neutrophils migrate to the lung in response to a chemotactic factor, where they then release mediators, such as GE or superoxide, that cause destruction of lung tissues.

There was no relationship between the GE-α1-PI level and the neutrophil count. Therefore the release of GE into the circulation is unrelated to an increase in circulating neutrophils. We found a significant correlation between the GE-α1-PI concentration and the amount of endotoxin in blood. In patients suffering from sepsis, endotoxin may stimulate neutrophils directly to release GE. Smedly et al.[19] demonstrated that neutrophils stimulated by a low concentration of lipopolysaccharide with C5a or chemotactic factor produced marked endothelial injury. They concluded that these factors caused the release of GE from neutrophils.

In this study the increase in GE-$\alpha$1-PI was significantly correlated with decreases in the levels of fibronectin and coagulation factor XIII. *In vitro*, GE has been shown to degrade various connective tissue components, including elastin, collagen, and proteoglycan,[20,21] as well as fibrinolytic and coagulation factors, complement, fibronectin, and some transport proteins.[22,23] Fibronectin, a glycoprotein, plays a major role in cell conjugation and cell-mediated tissue repair.[24] Fibronectin levels were within the normal range in our hemorrhagic shock patients but were significantly low in those with septic shock. In addition there was a significant negative correlation between the GE-$\alpha$1-PI level and that of fibronectin.

Coagulation factor XIII is an important factor in tissue repair.[25] Coagulation factor XIII was low in group 1 and was also significantly negatively related to levels of GE-$\alpha$1-PI. These findings suggest that GE may degrade these substrates *in vivo* and thereby cause tissue damage.

Severe tissue injury occurred in patients with septic shock complicated by MOF. In these patients fibronectin and coagulation factor XIII were decreased, in which case, tissue repair and regrowth could not be expected. Although $\alpha$1-PI increased and GE activity was inhibited in blood, GE activity was enhanced in BALF. These results suggest that GE plays a significant role in the local destruction of inflamed tissue and causes severe tissue damage in patients with septic shock and MOF.

## References

1. Fry DE, Pearlstein L, Fulton RL, et al. Multiple system organ failure: the role of uncontrolled infection. Arch Surg 1980; 115:136–140.
2. Eiseman B, Sloan R, Hansbrough J, et al. Multiple organ failure: clinical and experimental. Am Surg 1980; 46:14–19.
3. Carrico CJ, Meakins JL, Marshall JC, et al. Multiple-organ-failure syndrome. Arch Surg 1986; 121:196–208.
4. Weissmann G, Zurier RB, Hoffstein S. Leukocytic proteases and the immunologic release of lysosomal enzymes. Am J Pathol 1972; 68:539–559.
5. Fritz H, Jochum M, Duswald KH, et al. Granulocyte proteinases as mediators of unspecific proteolysis in inflammation. A review. *In* Proteinases in Inflammation and Tumor Invasion. New York: Walter De Gruyter, 1986, pp 1–24.
6. Janoff A. Elastase in tissue injury. Annu Rev Med 1985; 36:207–216.
7. Kaplan PD, Kuhn C, Pierce JA. The induction of emphysema with elastase. 1. The evolution of the lesion and the influence of serum. J Lab Clin Med 1973; 82:349–357.
8. Smith SF, Guz A, Cooke NT, et al. Extracellular elastolytic activity in human lung lavage: a comparative study between smokers and non-smokers. Clin Sci 1985; 69:17–27.
9. Adeyemi EO, Hull RG, Chadwick VS, et al. Circulating human leukocyte elastase in rheumatoid arthritis. Rheumatol Int 1986; 6:57–60.
10. Duswald KH, Jochum M, Fritz H, et al. Released granulocytic elastase: an indicator of pathobiochemical alterations in septicemia after abdominal surgery. Surgery 1985; 98:892–899.
11. Tanaka H, Yoshioka T, Sugimoto T, et al. A sensitive and specific assay for granulocyte elastase in inflammatory tissue fluid using L-pyroglutamyl-L-prolyl-L-valine-p-nitroanilide. Clin Chim Acta 1990; 187:173–180.
12. Sugimoto T, Ogawa M, Shimazaki S, et al. Klinische Untersuchung uber die Schockorgane in Beziehung zur Schockdauer. Anaesthesist 1976; 25:51–55.
13. Lee C, Fein AM, Lippmann M, et al. Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory-distress syndrome. N Engl J Med 1981; 304:192–196.
14. Goldfarb MA, Ciurej TF, McAslan TC, et al. Tracking respiratory therapy in the trauma patient. Am J Surg 1975; 129:255–258.
15. Ikegami K, Ikemura K, Sugimoto T, et al. Early diagnosis of invasive candidiasis and rapid evaluation of antifungal therapy by combined use of conventional chromogenic limulus test and a newly developed endotoxin specific assay. J Trauma 1988; 28:1118–1126.
16. Bohn H. Isolierung und Charakterisierung des fibrinstabilisierenden Faktors aus menschlichen Thrombozyten. Thrombos Diathes Haemorrh 1970; 23:454–468.
17. Ohlsson K, Olsson I. The neutral proteases of human granulocytes: isolation and partial characterization of granulocyte elastases. Eur J Biochem 1974; 42:519–527.
18. Carrell RW. $\alpha$1-Antitrypsin: molecular pathology, leukocytes, and tissue damage. J Clin Invest 1986; 78:1427–1431.
19. Smedly LA, Tonnesen MG, Worthen GS, et al. Neutrophil-mediated injury to endothelial cells: enhancement by endotoxin and essential role of neutrophil elastase. J Clin Invest 1986; 77:1233–1243.
20. Keiser H, Greenwald RA, Janoff A. Degradation of cartilage proteoglycan by human leukocyte granule neutral protease. A model of joint injury. II. Degradation of isolated bovine nasal cartilage proteoglycan. J Clin Invest 1976; 57:625–632.
21. Mainardi CL, Hasty DL, Kang AH. Specific cleavage of human type III collagen by human polymorphonuclear leukocyte elastase. J Biol Chem 1980; 255:12006–12010.
22. Jochum M, Witte J, Fritz H, et al. Clotting and other plasma factors in experimental endotoxemia: inhibition of degradation by exogenous proteinase inhibitors. Eur Surg Res 1981; 13:152–158.
23. Gramse M, Havemann K, Egbring R. Alpha-2-plasmin-inhibitor inactivation by human granulocyte elastase. Adv Exp Med Biol 1984; 167:253–261.
24. Mosher DF, Schad PE, Kleinman HK. Cross-linking of fibronectin to collagen by blood coagulation factor XIII. J Clin Invest 1979; 64:781–787.
25. Mosher DF. Action of fibrin-stabilizing factor on cold-insoluble globulin and $\alpha$2-macroglobulin in clotting plasma. J Biol Chem 1976; 251:1639–1645.

# BOOK REVIEWS

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**Cardiac Transplantation.** Mark E. Thompson. 271 pp. Philadelphia: F. A. Davis, 1989. $75.00.

THIS TEXT IS part of the *Cardiovascular Clinic Series* and represents an up-to-date review of the entire subject of cardiac transplantation, provided by distinguished leaders in the field. No longer is heart transplantation an experimental entity in the treatment of end-stage heart disease, as outlined by the editor, Mark Thompson, in the preface. He states 'The procedure has progressed from one of limited experimental availability . . . to one that is generally accepted as a suitable alternative for the management of refractory congestive heart failure, now limited by a suitable number of donors.'

The book provides a concise but comprehensive summary of the entire scope of cardiac transplantation. It is clinically oriented and well illustrated with figures and tables that are easy to follow and understand. The organization of the text is superb, beginning with an historical review of heart and heart–lung transplantation in Part 1. Part 2 reviews the basic scientific mechanisms dealing with the physiology, pathology, and immunology of the transplanted organ. All of the many clinical aspects of the procedure are covered in Part 3, including preoperative patient preparation, operative technique, and postoperative complications. Finally Part 4 addresses special problems encountered in the specialty, such as pediatric cardiac transplantation and multiorgan transplantation.

The bibliography at the end of each chapter is complete and up-to-date.

This text should be available to all physicians and paramedical personnel involved in cardiac transplantation. It is both detailed and comprehensive enough for those dealing with the subject on a daily basis, while providing valuable guidance to those less familiar with the specialty or those instituting a new program.

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**The International Textbook of Cardiology.** Tsung O. Cheng. 1299 pp. Elmsford, NY: Pergamon Press, 1986. $87.50.

THE USE OF the word 'international' in the title of this multiauthored textbook edited by Dr. Tsung O. Cheng is entirely appropriate. Published by the Pergamon Press in softcover, Dr. Cheng has assembled a truly international group of authors. Approximately 70% of the authors are from the United States but Canada, Europe, Africa, South American, and particularly the Mid and Far East also are represented. As stated in the preface, Dr. Cheng had three goals in compiling this text: (1) to present an up-to-date treatise on modern cardiology from a global perspective; (2) to call on the expertise of authorities from around the world; and (3) to highlight important international differences in cardiovascular disease. He succeeds admirably in meeting these goals.

As with any multiauthored textbook, the quality of the chapters vary somewhat but, in general, most are well done, with useful supplemental illustrations. Some chapters, particularly by non-United States authors, give a genuinely global perspective on historical development and are 'state of the art' (to 1986). Some authors (and I am chagrined to note that they are mostly from the United States) give a much narrower view, heavily biased toward their own observations (*e.g.*, 80% or more of the cited references allude to their own work). In general, however, this is uncommon. I particularly liked the first several chapters on the epidemiology of heart disease in general and in the Far East. Chou's chapter on the ECG and VCG (I still think that the latter has value in teaching us to understand the ECG) are well done. The chapters on noninvasive cardiac imaging and congenital heart disease (in young and in adult patients) are concise, comprehensive, and well organized. Barlow's chapter on mitral valve 'billowing and prolapse' was interesting from an historical perspective and relatively well balanced, although it is obvious that he believes there is an associated 'syndrome.' Many of the cited disease and symptom associations are not standing up to more rigorous case-controlled analyses. The section on arrhythmias was complete and clearly written. Similarly the section on coronary artery disease (CAD) was well balanced. The chapter on coronary spasm gives the perspective from an area of the world where it occurs commonly in the absence of atherosclerosis. The chapter on surgical treatment was similarly comprehensive and fairly well balanced, alluding to areas of controversy when appropriate. One might have wished that the authors had presented data from the randomized cooperative trials separately and with side-by-side comparisons of medical *versus* surgical results. The section on thrombolytic therapy was written by one of its pioneers and the chapters on cardiomyopathy are truly global and written by experts in their field. Hancock's chapter on the pericardium and Neu's chapter on endocarditis are well done also. Several chapters deal with the relation between the heart and other systems (the GI tract, the endocrine system, the cardiovascular affects of pregnancy, hematology/oncology, connective-tissue diseases, neuropsychiatric disorders, and renal disease.) These are written, for the most part, by noncardiologists and they provide a valuable perspective. The chapter on cardiovascular pharmacology is relatively current, given the date of publication. The chapters on herbal pharmacology and acupuncture anesthesia are interesting and are complimented by parallel 'scientific' chapters. Stamler's chapter on preventive cardiology is toward the end of the book and one might argue that, just as this should be a primary emphasis in the home, schools, community, and workplace so should these data be presented earlier in the book. They would nicely complement the chapters on epidemiology. The chapter on cardiovascular nursing is recommended and the chapter on the relationship between the cardiologist and the pharmaceutical industry is a 'must', particularly for those in academia or who are involved in clinical trials of new agents.

Some of the problems of the book relate to the 1986 publication date. (It was not received by this journal until late 1988 and an additional delay was induced by this reviewer; for the latter, I apologize). The more extensive experience with thrombolytic therapy, PTCA, color-flow Doppler imaging, the CAST results, and the clinical implementation of new devices, such as the AICD, are a few more obvious examples. I can only hope that Dr. Cheng has been at work on the next edition. I also missed having chapters dedicated to an occasional topic such as the 'generic' aspects of either valvular heart disease or even specific valvular diseases. The data are there but are scattered in different sections.

From a global perspective on heart disease, however, these shortcomings are minor and there is more than ample worth, as the text now stands, to recommend it to medical students, postgraduate trainees, and physicians both in general practice as well as in the specialized care of patients with heart disease.

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**Neonatal Surgery, 3rd Edition.** James Lister and Irene M. Irving. 733 pp. Stoneham, MA: Butterworths, 1990. $185.00.

WITHIN THE 700 TEXT pages of this book are contributions drawing almost exclusively from the staff at the Royal Liverpool Children's Hospital at Alder Hey. It is divided into eight parts and has 51 chapters that provide excellent coverage of neonatal surgical problems. Part 1 provides almost 100 pages of a superb general review of topics that concern those who care for the surgical neonate. Chapters on ethics, genetics, neonatal physiology, and infections are included, as is a review of antenatal diagnosis and its relevance to pediatric surgeons. Parts 2, 3, 4, 6, and 8 cover topics germane to the general day-to-day practice of pediatric surgery, including the head and neck, thoracic, abdominal, and urogenital sections. Within these parts are chapters on birth trauma and the various tumors presenting during the neonatal period. The chapters all conform to the general format of a brief historical note followed by a relevant section on anatomy and embryology. Pathophysiology, as appropriate, is reviewed, as is clinical presentation and management/treatment issues. Included in parts 5 and 7 are superb discussions on cardiac and neurosurgical conditions of infancy, which are excellent sections for nonspecialists who wish to know more about these aspects of newborn surgery. An extensive bibliography follows every chapter, with key references to the European and American literature.

To best appreciate this book a clear understanding of what it is and is not is needed. The book is a well-organized, beautifully written, and satisfactorily presented compendium of newborn surgical problems. Its standardization of chapter format makes for easy use and reference. Its size is not large by comparison to many current medical textbooks and thus could be viewed easily as 'portable.' The book is not a textbook of pediatric surgery—and does not pretend to be. Its mission is to cover only topics germane to the neonate; thus issues relevant to the care of toddlers, children, and adolescents are not covered. This cannot be viewed as a singular reference for surgical conditions of childhood. The book is not an atlas of surgery nor nearly detailed enough in its discussion of surgical technique to be used as a primary reference by a pediatric surgical fellow or practitioner who must learn a technique that is new or unfamiliar.

*Neonatal Surgery* is moderately expensive and most definitely is not the book to have if, as a student, resident, or general surgeon, a single reference book on pediatric surgery is wanted. On the other hand, if one deals only with neonates, this would be the single book to have and I would recommend that all neonatologists give strong consideration to purchasing a copy. Furthermore a book like this belongs in any newborn intensive care nursery as well as in a library of any institution that cares for sick neonates. Practicing pediatric surgeons may find that the book does not add much to information available to them in the major tomes of pediatric surgery but, on the other hand, may find the book to be refreshing reading as well as a fine volume to loan to the many rotating students and residents on service looking for an easy-to-digest reference on a topic in neonatal surgery. For the trainee in pediatric surgery, the book's size, readability, and generally excellent bibliography make the text a worthy investment.

With the book's virtues and limitations in mind, I could not more heartily recommend its acquisition because the editors have done a superb job in realizing the objectives of the book.

ARTHUR J. ROSS III, M.D.
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**Atlas of Nutritional Support Techniques.** John L. Rombeau, Michael D. Caldwell, Loretta Forlaw, and Peggi A. Guenter. 368 pp. Boston: Little, Brown and Co., 1989. $34.50.

THIS ATLAS IS THE first composite reference to procedures and techniques currently used in the delivery of enteral and parenteral nutrition. The authors have done a superb job in developing each subject from a basic concept point of view, with explicit illustrations for those first attempting a procedure, to discussions of advanced nuances for the more experienced reader. Each section reviews indications and purposes, necessary equipment, technique of application, on-going care, and potential complications and provides pertinent references for further study.

The first section of the atlas reviews techniques of anthropometric and metabolic nutritional assessment. The section dealing with metabolic assessment is of special interest in current practice. The second section presents an excellent review of enteral nutrition techniques, including nasoenteral tube feeding, feeding by tube enterostomy, and home enteral nutrition. The third section is perhaps the strongest. It outlines techniques of parenteral nutrition with discussions of vascular access, including peripheral and central venous cannulation, venous cutdown, selection and use of infusion control devices, evaluation of episodes of potential catheter sepsis, changing of catheters over guidewires, management of permanent central venous catheters, compounding of intravenous nutrition solutions, and evaluation of various complications of parenteral nutrition. The fourth section reviews current approaches to gastric surgery for morbid obesity. This section appears out of context with the rest of the atlas because it is addressed superficially and deals only with the surgical approach to obesity. It provides the reader with only a working familiarity of the subject matter.

The authors have clearly succeeded in developing a functionally useful atlas. It will find its place as a handy reference for all those interested in or responsible for the management of nutritional support.

JOHN P. GRANT, M.D.
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**Bowel Obstruction: Differential Diagnosis and Clinical Management.** John P. Welch. 736 pp. Philadelphia: WB Saunders, 1990. $95.00.

DR. WELCH AND HIS nine collaborators from the University of Connecticut have produced a thoroughly documented, yet remarkably readable volume on the subject of bowel obstruction. The chapter on history of bowel obstruction is exceptionally detailed, with more than 400 references for the interested student to pursue. Other chapters on various aspects of large and small bowel obstruction are equally well documented, including up-to-date discussions of experimental studies such as those directed at the prevention of adhesions. The chapter on intestinal intubation is a delightful mix of history and current management. The radiographs, which are so critical to the complete discussion of intestinal obstruction, are numerous, modern, and clearly reproduced. The illustrations are a mixture of those published by permission and original drawings and are also well reproduced. Each chapter is well indexed at the front and the strong organization in this book is apparent. It is a most complete, modern, and readable discussion of the spectrum of intestinal obstruction. It is difficult to identify any major deficiency in this volume. It is a worthy successor to the classical treatise on the subject and should find wide acceptance in the libraries of institutions and individuals alike.

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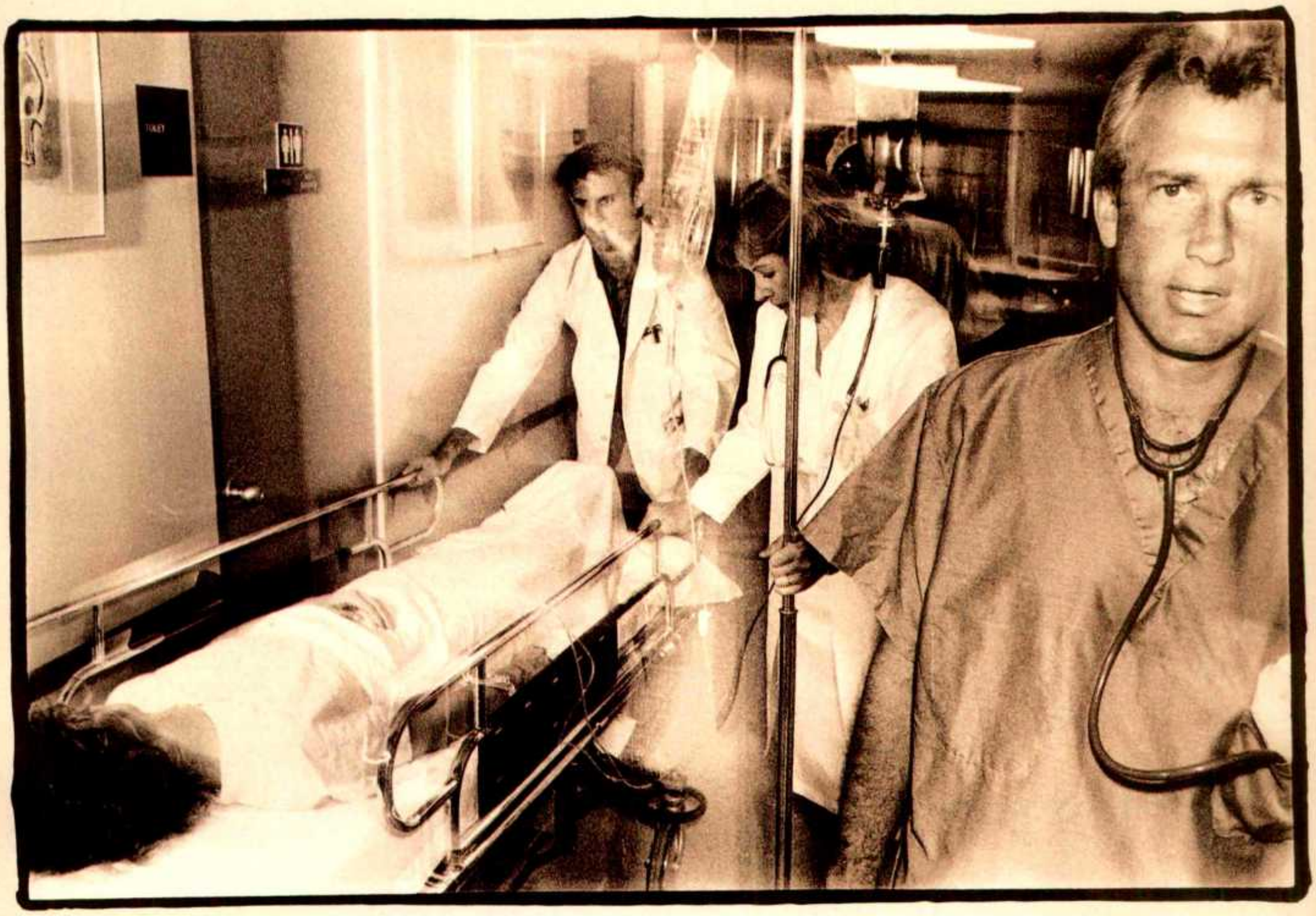

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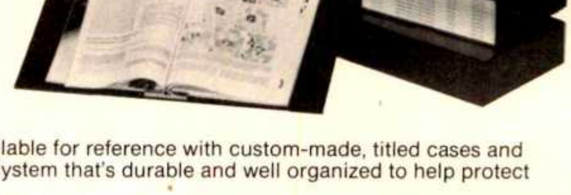

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**References:**

**1**. Data available on request from Roerig. **2**. Aldridge KE, Sanders CV, Marier RL: Variation in the potentiation of β-lactam antibiotic activity by clavulanic acid and sulbactam against multiply antibiotic-resistant bacteria. *J Antimicrob Chemother* 1986;17:463-469. **3**. Crombleholme WR, Ohm-Smith M, Robbie MO, et al: Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. *Am J Obstet Gynecol* 1987;156(Feb):507-512. **4**. Cucharal G, Snydman D, Jacobus N, et al: Comparison of new antimicrobial agents against the *Bacteroides fragilis* group. Abstract, presented at the Annual Meeting of the American Society of Microbiology, Miami Beach, Fla; May 1988. **5**. D'Amato RF, Hochstein L, Pavia M: *In vitro* susceptibilities of aerobic and anaerobic clinical isolates to ampicillin/sulbactam. Presented as a Scientific Exhibit at the 87th Annual Meeting of the American Society of Microbiology, Atlanta, March 1987. **6**. Finegold SM: Anaerobic bacteria: Their role in infection and their management. *Postgrad Med* 1987;81(8):141-147. **7**. Jenkins SG: Susceptibility patterns of *Bacteroides fragilis* group isolates to ampicillin/sulbactam and other selected antibiotics. Presented at a symposium entitled *Ampicillin/Sulbactam: New Strategy for the Treatment of Infectious Disease*. Montreux, Switzerland, July 16-17, 1987, pp 19-20. **8**. Tally FP, Jacobus NV: Activity of sulbactam against recent isolates of aerobic and anaerobic bacteria, abstract 36. Presented at the 23rd International Congress of Antimicrobial Agents and Chemotherapy, Las Vegas, Oct 24-26, 1983 (abs). **9**. Wasilauskas B: Susceptibility of anaerobes to ampicillin-sulbactam and 6 other antimicrobial agents, abstract. Presented at the Annual Meeting of the American Society for Microbiology, Miami Beach, Fla; May 8-13, 1988. **10**. Wexler HM, Harris B, Carter WT, et al: In vitro efficacy of sulbactam combined with ampicillin against anaerobic bacteria. *Antimicrob Agents Chemother* 1985;27:876-878. **11**. Ampicillin/sulbactam (Unasyn). *Med Lett Drugs Ther* 1987;29(August 28):79-81. **12**. Hemsell DL, Wendel GD, Hemsell PG: Combating beta-lactamase enzyme—principal defense mechanism of many pelvic infection pathogens. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **13**. Senft H-H, Stiglmayer R, Eibach HW, et al: Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. *Drugs* 1986;31(suppl 2):18-21. **14**. Newton ER, Gibbs RS: Treatment of postpartum endometritis: A comparison of ampicillin/sulbactam vs. gentamicin plus clindamycin. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **15**. Gunning J: A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. *Drugs* 1986;31(suppl 2):14-17. **16**. Stromberg BV, Reines HD, Hunt P: Comparative clinical study of sulbactam and ampicillin and clindamycin and tobramycin in infections of soft tissues. *Surg Gyn Obstet* 1986;162:575-578. **17**. Kager L, Malmborg AS, Nord CE, et al: A randomized controlled trial of ampicillin plus sulbactam vs. gentamicin plus clindamycin in the treatment of intraabdominal infections: A preliminary report. *Rev Infect Dis* 1986;8(suppl 5):S583-S588. **18**. Bruhat MA, Pouly JL, Le Boedec G, et al: Treatment of acute salpingitis with sulbactam/ampicillin: Comparison with cefoxitin. *Drugs* 1986;31(suppl 2):7-10. **19**. Faro S: Experience with ampicillin/sulbactam for OB/GYN infections. Presented at a symposium entitled *β-Lactamase Inhibitors: Progress with Ampicillin/Sulbactam*. Atlanta, December 6, 1987, p 14 (abs).

### INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

**Skin and Skin Structure Infections** caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

**Intra-Abdominal Infections** caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

**Gynecological Infections** caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

### CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

### WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

### PRECAUTIONS

**General**: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

**Drug Interactions**: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

**Drug/Laboratory Test Interactions**: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

**Pregnancy**

**Pregnancy Category B**: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

**Labor and Delivery**: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Nursing Mothers**: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

**Pediatric Use**: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

### ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

**Local Adverse Reactions**

Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%

**Systemic Adverse Reactions**

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

**Adverse Laboratory Changes**

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

*Hepatic*: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
*Hematologic*: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
*Blood Chemistry*: Decreased serum albumin and total proteins.
*Renal*: Increased BUN and creatinine.
*Urinalysis*: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

**Gastrointestinal**: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

**Hypersensitivity Reactions**: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

**Hematologic**: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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**References**:
**1.** Data available on request from Roerig. **2.** Aldridge KE, Sanders CV, Marier RL: Variation in the potentiation of β-lactam antibiotic activity by clavulanic acid and sulbactam against multiply antibiotic-resistant bacteria. *J Antimicrob Chemother* 1986;17:463-469. **3.** Crombleholme WR, Ohm-Smith M, Robbie MO, et al: Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. *Am J Obstet Gynecol* 1987;156(Feb):507-512. **4.** Cucharal G, Snydman D, Jacobus N, et al: Comparison of new antimicrobial agents against the *Bacteroides fragilis* group. Abstract, presented at the Annual Meeting of the American Society of Microbiology, Miami Beach, Fla, May 1988. **5.** D'Amato RF, Hochstein L, Pavia M: *In vitro* susceptibilities of aerobic and anaerobic clinical isolates to ampicillin/sulbactam. Presented as a Scientific Exhibit at the 87th Annual Meeting of the American Society of Microbiology, Atlanta, March 1987. **6.** Finegold SM: Anaerobic bacteria: Their role in infection and their management. *Postgrad Med* 1987;81(8):141-147. **7.** Jenkins SG: Susceptibility patterns of *Bacteroides fragilis* group isolates to ampicillin/sulbactam and other selected antibiotics. Presented at a symposium entitled *Ampicillin/Sulbactam: New Strategy for the Treatment of Infectious Disease*. Montreux, Switzerland, July 16-17, 1987, pp 19-20. **8.** Tally FP, Jacobus NV: Activity of sulbactam against recent isolates of aerobic and anaerobic bacteria, abstract 36. Presented at the 23rd International Congress of Antimicrobial Agents and Chemotherapy, Las Vegas, Oct 24-26, 1983 (abs). **9.** Wasilauskas B: Susceptibility of anaerobes to ampicillin-sulbactam and 6 other antimicrobial agents, abstract. Presented at the Annual Meeting of the American Society for Microbiology, Miami Beach, Fla, May 8-13, 1988. **10.** Wexler HM, Harris B, Carter WT, et al: In vitro efficacy of sulbactam combined with ampicillin against anaerobic bacteria. *Antimicrob Agents Chemother* 1985;27:876-878. **11.** Ampicillin/sulbactam (Unasyn). *Med Lett Drugs Ther* 1987;29(August 28):79-81. **12.** Hemsell DL, Wendel GD, Hemsell PG: Combating beta-lactamase enzyme—principal defense mechanism of many pelvic infection pathogens. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **13.** Senft H-H, Stiglmayer R, Eibach HW, et al: Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. *Drugs* 1986;31(suppl 2):18-21. **14.** Newton ER, Gibbs RS: Treatment of postpartum endometritis: A comparison of ampicillin/sulbactam vs. gentamicin plus clindamycin. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **15.** Gunning J: A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. *Drugs* 1986;31(suppl 2):14-17. **16.** Stromberg BV, Reines HD, Hunt P: Comparative clinical study of sulbactam and ampicillin and clindamycin and tobramycin in infections of soft tissues. *Surg Gyn Obstet* 1986;162:575-578. **17.** Kager L, Malmborg AS, Nord CE, et al: A randomized controlled trial of ampicillin plus sulbactam vs. gentamicin plus clindamycin in the treatment of intraabdominal infections: A preliminary report. *Rev Infect Dis* 1986;8(suppl 5):S583-S588. **18.** Bruhat MA, Pouly JL, Le Boedec G, et al: Treatment of acute salpingitis with sulbactam/ampicillin: Comparison with cefoxitin. *Drugs* 1986;31(suppl 2):7-10. **19.** Faro S: Experience with ampicillin/sulbactam for OB/GYN infections. Presented at a symposium entitled *β-Lactamase Inhibitors: Progress with Ampicillin/Sulbactam*. Atlanta, December 6, 1987, p 14 (abs).

**INDICATIONS AND USAGE**
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
**Skin and Skin Structure Infections** caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*
**Intra-Abdominal Infections** caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
**Gynecological Infections** caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.
**CONTRAINDICATIONS**
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.
**WARNINGS**
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.
**PRECAUTIONS**
**General**: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
**Drug Interactions**: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
**Drug/Laboratory Test Interactions**: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
**Carcinogenesis, Mutagenesis, Impairment of Fertility**: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
**Pregnancy**
**Pregnancy Category B**: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
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**Nursing Mothers**: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
**Pediatric Use**: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.
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Thrombophlebitis—3%
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Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
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*Hematologic*: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
*Blood Chemistry*: Decreased serum albumin and total proteins.
*Renal*: Increased BUN and creatinine.
*Urinalysis*: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
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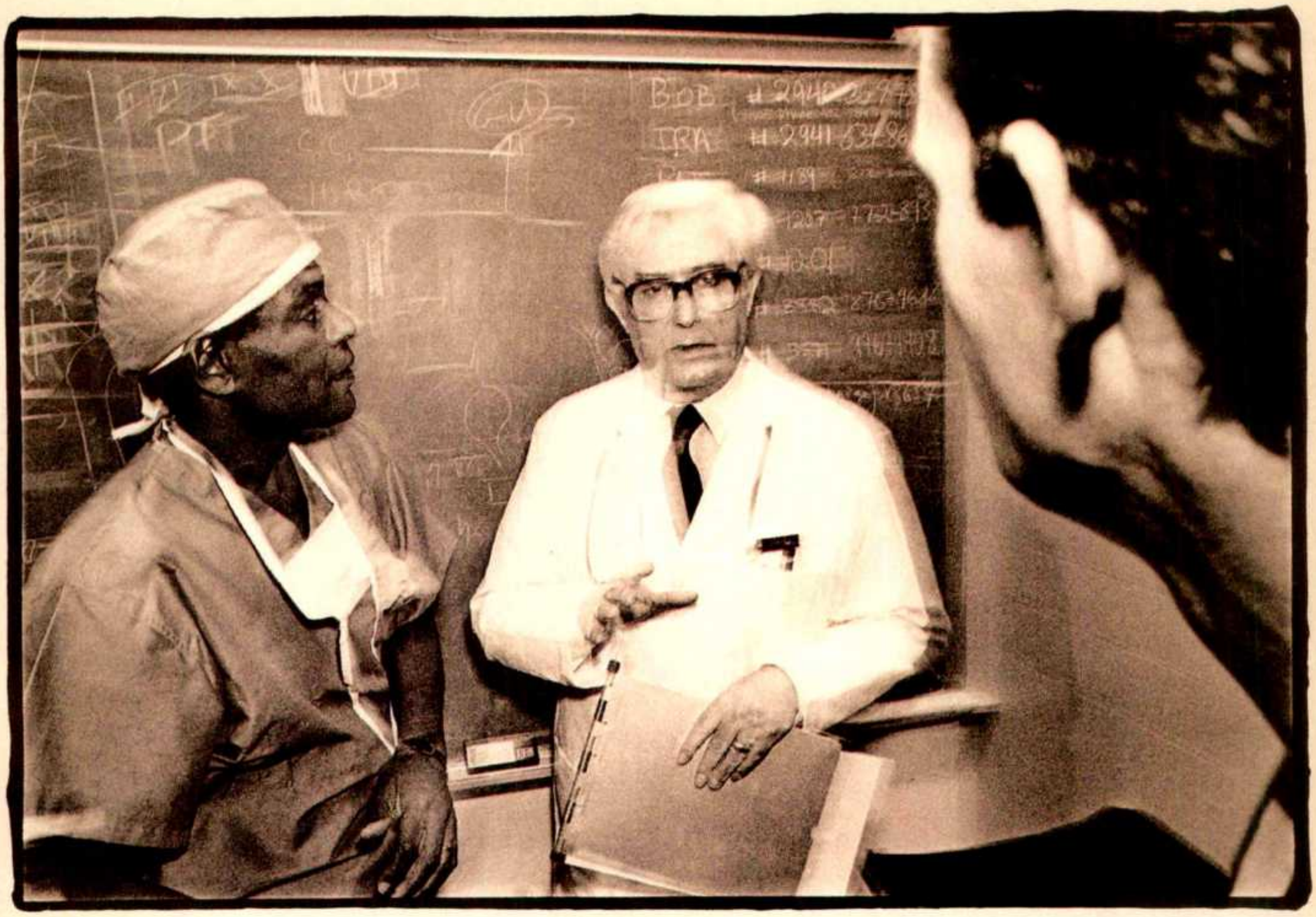

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## SUMMARY OF REQUIREMENTS

Type manuscript double spaced, including title page, abstract, text, acknowledgments, references, tables, and legends.

Each manuscript component should begin on a new page, in this sequence:

Title page
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Tables: each table, complete with title and footnotes, on a separate page
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Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in.), but no larger than 20.3 by 25.4 cm (8 by 10 in.).

Submit the required number of copies of manuscript and figures (*see* journal's instructions) in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, as described in Submission of Manuscripts, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

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Type manuscript on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in. or 8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in.). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations. Begin each of the following sections on separate pages: title page, mini abstract, abstract, text, acknowledgments, references, individual tables, and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Manuscripts will be reviewed for possible publication with the understanding that they are being submitted to one journal at a time and have not been published, simultaneously submitted, or already accepted for publication elsewhere. This does not preclude consideration of a manuscript that has been rejected by another journal or of a complete report that follows publication of preliminary findings elsewhere, usually in the form of an abstract. Copies of any possibly duplicative published material should be submitted with the manuscript that is being sent for consideration.

### TITLE PAGE

The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (counting letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

### MINI ABSTRACT

A short description of the study should be submitted to appear on the table of contents. It should consist of approximately three sentences of no more than 50 words.

### ABSTRACT

The second page should carry an abstract of not more than 150 words. The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals and observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations. Use only approved abbreviations (*see* list of Commonly Used Approved Abbreviations elsewhere in this document).

### TEXT

The text of observational and experimental articles is usually, but not necessarily, divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials may need other formats, and authors should consult individual journals for further guidance.

*Introduction:* Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

*Methods:* Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like sometimes may be suitably presented in the form of one or more appendixes.

*Results:* Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

*Discussion:* Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

### ACKNOWLEDGMENTS

Acknowledge only persons who have made substantive contributions to the study. Authors are responsible for obtaining written permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions.

### REFERENCES

Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parenthesis). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section, which has been approved by the National Library of Medicine.

The titles of journals should be abbreviated according to the style used in *Index Medicus*. A list of abbreviated names of frequently cited journals is given near the end of this document; for others, consult the List of Journals Indexed, printed annually in the January issue of *Index Medicus*.

Avoid using abstracts as references; unpublished observations and personal communications may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

The references must be verified by the author(s) against the original documents.

Examples of correct forms of references are given below.

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1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al.)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976; 294:687–690.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gammaglutamyltransferase in blood. Scand J Clin Lab Invest 1976; 36:119–125.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976; 5:224–225.

*Books and Other Monographs*

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–471.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

*Other Articles*

8. Newspaper Article

   Shaffer RA. Advances in chemistry are starting to unlock mysteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12:1(col. 1), 10(col. 1).

9. Magazine Article

   Roueché B. Annals of medicine: the Santa Claus culture. The New Yorker 1971 Sep 4:66–81.

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### COMMONLY USED APPROVED ABBREVIATIONS

#### *Standard Units of Measurement*

| Term | Abbreviation or Symbol |
|---|---|
| ampere | A |
| ångström | Å |
| barn | b |
| candela | cd |
| coulomb | C |
| counts per minute | cpm |
| counts per second | cps |
| curie | Ci |
| degree Celsius | °C |
| disintegration per minute | dpm |
| disintegration per second | dps |
| electron Volt | eV |
| equivalent | Eq |
| farad | F |
| gauss | G |
| gram | g |
| henry | H |
| hertz | Hz |
| hour | h |
| international unit | IU |
| joule | J |
| kelvin | K |
| kilogram | kg |
| liter | L |
| meter, metre | m |
| minute | min |
| molar | mol/L |
| mole | mol |
| newton | N |
| normal (concentration) | N |
| ohm | Ω |
| osmol | osmol |
| pascal | Pa |
| revolutions per minute | rpm |
| second | s |
| square centimeter | $cm^2$ |
| volt | V |
| watt | W |
| week | wk |
| year | yr |

#### *Combining Prefixes*

| | | |
|---|---|---|
| tera- | ($10^{12}$) | T |
| giga- | ($10^{9}$) | G |
| mega- | ($10^{6}$) | M |
| kilo- | ($10^{3}$) | k |
| hecto- | ($10^{2}$) | h |
| deca- | ($10^{1}$) | da |
| deci- | ($10^{-1}$) | d |
| centi- | ($10^{-2}$) | c |
| milli- | ($10^{-3}$) | m |
| micro- | ($10^{-6}$) | μ |
| nano- | ($10^{-9}$) | n |
| pico- | ($10^{-12}$) | p |
| femto- | ($10^{-15}$) | f |
| atto- | ($10^{-18}$) | a |

#### *Statistical Terms*

| | |
|---|---|
| correlation coefficient | r |
| degrees of freedom | df |
| mean | $\bar{x}$ |
| not significant | NS |

| | |
|---|---|
| number of observations | n |
| probability | p |
| standard deviation | SD |
| standard error of the mean | SEM |
| "Student's" t test | *t* test |
| variance ratio | F |

### *Others*

| | |
|---|---|
| adenosinediphosphatase | ADPase |
| adenosine 5′-diphosphate (adenosine diphosphate) | ADP |
| adenosine 5′-monophosphate (adenosine monophosphate, adenylic acid) | AMP |
| adenosine triphosphatase | ATPase |
| adenosine 5′-triphosphate (adenosine triphosphate) | ATP |
| adrenocorticotropic hormone (adrenocorticotropin) | ACTH |
| bacille Calmette-Guérin | BCG |
| basal metabolic rate | BMR |
| body temperature, pressure, and saturated | BTPS |
| central nervous system | CNS |
| coenzyme A | coA |
| deoxyribonucleic acid (deoxyribonucleate) | DNA |
| dihydroxyphenethylamine | dopamine |
| electrocardiogram | ECG |
| electroencephalogram | EEG |
| enteric cytopathogenic human orphan (virus) | ECHO |
| ethyl | Et |
| ethylenediaminetetraacetate | EDTA |
| gas-liquid chromatography | GLC |
| guanosine 5′-monophosphate (guanosine monophosphate, guanylic acid) | GMP |
| hemoglobin | Hb |
| logarithm (to base 10; common logarithm) | log |
| logarithm, natural | ln |
| methyl | Me |
| Michaelis constant | $K_m$ |
| negative logarithm of hydrogen ion activity | pH |
| partial pressure of $CO_2$ | $P_{CO_2}$ |
| partial pressure of $O_2$ | $P_{O_2}$ |
| per | / |
| percent | % |
| radiation (ionizing, absorbed dose) | rad |
| respiratory quotient | RQ |
| specific gravity | sp gr |
| standard atmosphere | atm |
| standard temperature and pressure | STP |
| ultraviolet | uv |
| volume | vol |
| volume ratio (volume per volume) | vol/vol |
| weight | wt |
| weight per volume | wt/vol |
| weight ratio (weight per weight) | wt/wt |

## ABBREVIATIONS OF NAMES OF FREQUENTLY CITED JOURNALS

| | |
|---|---|
| Acta Medica Scandinavica | Acta Med Scand |
| American Family Physician | Am Fam Physician |
| American Heart Journal | Am Heart J |
| American Journal of Cardiology | Am J Cardiol |
| American Journal of Clinical Nutrition | Am J Clin Nutr |
| American Journal of Clinical Pathology | Am J Clin Pathol |
| American Journal of Digestive Diseases | Am J Dig Dis |
| American Journal of Diseases of Children | Am J Dis Child |
| American Journal of Human Genetics | Am J Hum Genet |
| American Journal of the Medical Sciences | Am J Med Sci |
| American Journal of Medicine | Am J Med |
| American Journal of Obstetrics and Gynecology | Am J Obstet Gynecol |
| American Journal of Ophthalmology | Am J Ophthalmol |
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| American Journal of Physical Medicine | Am J Phys Med |
| American Journal of Physiology | Am J Physiol |
| American Journal of Psychiatry | Am J Psychiatry |
| American Journal of Public Health | Am J Public Health |
| American Journal of Roentgenology | AJR |
| American Journal of Surgery | Am J Surg |
| American Journal of Tropical Medicine and Hygiene | Am J Trop Med Hyg |
| American Review of Respiratory Disease | Am Rev Respir Dis |
| Anaesthesia | Anaesthesia |
| Anesthesiology | Anesthesiology |
| Annals of Allergy | Ann Allergy |
| Annals of Internal Medicine | Ann Intern Med |
| Annals of Otology, Rhinology and Laryngology | Ann Otol Rhinol Laryngol |
| Annals of Surgery | Ann Surg |
| Annals of Thoracic Surgery | Ann Thorac Surg |
| Archives of Dermatology | Arch Dermatol |
| Archives of Environmental Health | Arch Environ Health |
| Archives of General Psychiatry | Arch Gen Psychiatry |
| Archives of Internal Medicine | Arch Intern Med |
| Archives of Neurology | Arch Neurol |
| Archives of Ophthalmology | Arch Ophthalmol |
| Archives of Otolaryngology | Arch Otolaryngol |
| Archives of Pathology and Laboratory Medicine | Arch Pathol Lab Med |
| Archives of Physical Medicine and Rehabilitation | Arch Phys Med Rehabil |
| Archives of Surgery | Arch Surg |
| Arthritis and Rheumatism | Arthritis Rheum |
| Blood; Journal of Hematology | Blood |
| Brain; Journal of Neurology | Brain |
| British Heart Journal | Br Heart J |
| British Journal of Obstetrics and Gynaecology | Br J Obstet Gynaecol |
| British Journal of Radiology | Br J Radiol |
| British Journal of Surgery | Br J Surg |
| British Medical Journal | Br Med J |
| Canadian Journal of Public Health | Can J Public Health |
| Canadian Medical Association Journal | Can Med Assoc J |
| Cancer | Cancer |
| Chest | Chest |
| Circulation; Journal of the American Heart Association | Circulation |
| Circulation Research | Circ Res |
| Clinical Pediatrics | Clin Pediatr (Phila) |
| Clinical Pharmacology and Therapeutics | Clin Pharmacol Ther |
| Clinical Science and Molecular Medicine | Clin Sci Mol Med |
| Clinical Toxicology | Clin Toxicol |
| Diabetes | Diabetes |
| DM, Disease-a-Month | DM |
| Endocrinology | Endocrinology |
| Gastroenterology | Gastroenterology |
| Geriatrics | Geriatrics |
| Gut | Gut |
| Human Pathology | Hum Pathol |
| Investigative Radiology | Invest Radiol |
| JAMA; Journal of the American Medical Association | JAMA |
| Journal of Allergy and Clinical Immunology | J Allergy Clin Immunol |
| Journal of Applied Physiology | J Appl Physiol |
| Journal of Biological Chemistry | J Biol Chem |
| Journal of Bone and Joint Surgery; American Volume | J Bone Joint Surg [Am] |
| Journal of Bone and Joint Surgery; British Volume | J Bone Joint Surg [Br] |
| Journal of Clinical Endocrinology and Metabolism | J Clin Endocrinol Metab |
| Journal of Clinical Investigation | J Clin Invest |
| Journal of Clinical Pathology | J Clin Pathol |
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| Journal of Laboratory and Clinical Medicine | J Lab Clin Med |
| Journal of Laryngology and Otology | J Laryngol Otol |
| Journal of Medical Education | J Med Educ |
| Journal of Nervous and Mental Disease | J Nerv Ment Dis |
| Journal of Neurosurgery | J Neurosurg |
| Journal of Pathology | J Pathol |
| Journal of Pediatrics | J Pediatr |
| Journal of Physiology | J Physiol |
| Journal of Thoracic and Cardiovascular Surgery | J Thorac Cardiovasc Surg |
| Journal of Trauma | J Trauma |
| Journal of Urology | J Urol |
| Lancet | Lancet |
| Medical Clinics of North America | Med Clin North Am |
| Medical Letter on Drugs and Therapeutics | Med Lett Drugs Ther |
| Medicine (Baltimore) | Medicine (Baltimore) |
| New England Journal of Medicine | N Engl J Med |
| Obstetrics and Gynecology | Obstet Gynecol |
| Pediatrics Clinics of North America | Pediatr Clin North Am |
| Pediatrics | Pediatrics |
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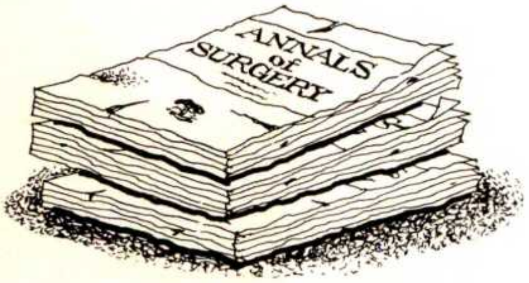

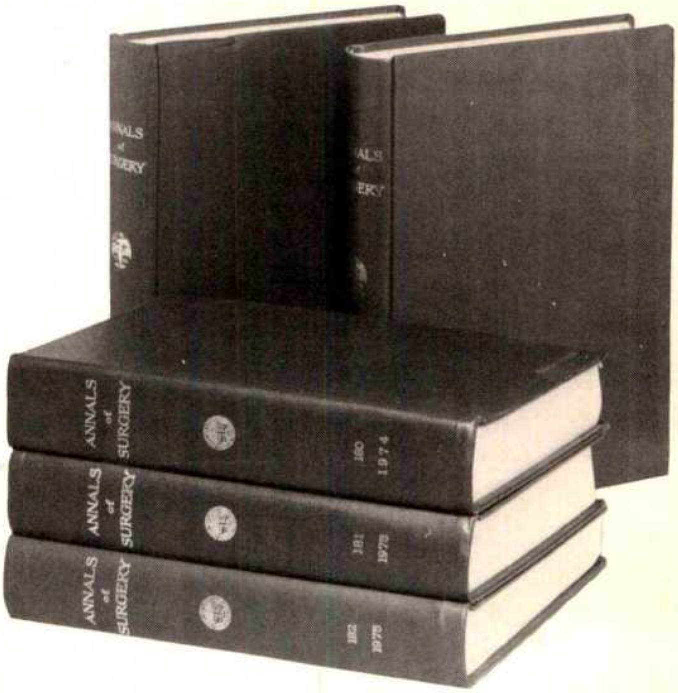

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EDITORIAL

# Carcinoembryonic Antigen

## *New Applications for an Old Marker*

JEFFREY A. NORTON, M.D.

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TUMOR MARKERS ARE circulating factors that are measurable in biologic fluids of patients with cancer and serve as a marker of the disease state. In 1965 Gold and Freedman demonstrated that a fetal antigen (carcinoembryonic antigen, CEA) was present in extracts of tumors from the gastrointestinal tract and fetal gut tissue but not in extracts of adult intestinal tissue. Subsequently this antigen was detected in the circulation of patients with gastrointestinal cancer, but not in the circulation of patients with nonmalignant conditions.[1] Despite these auspicious beginnings and the fact that radioimmunoassay, enzyme-linked immunoassay, and other immunologic assays can detect minute amounts of tumor markers accurately and reproducibly, tumor markers have not been as useful in the clinical practice of oncology as the initial studies suggested they would be.

The potential use of a circulating tumor marker includes screening of populations at risk for the development of tumor, unequivocal diagnosis of the presence of tumor, prognosis, assessment of therapeutic efficacy, and detection of residual or recurrent cancer. Currently the performance of available tumor markers as screening tests for the diagnosis of malignancy in high-risk individuals has been inadequate because of reduced sensitivity and occasional false-positive results. For example the use of serum levels of CEA in individuals with polyposis coli or ulcerative colitis has not detected reliably the presence of small, curable colon cancer.[2] Preoperative serum levels of carcinoembryonic antigen do appear to have important prognostic information; in general studies indicate that the higher the preoperative serum level of this marker the worse the patient's prognosis.[1,2] Current, exciting experimental research may provide new insights as to why high CEA production by tumors is associated with increased tumor growth[3] and poorer prognosis.[1,2] Carcinoembryonic antigen functions to modulate intercellular adhesion[4] and as an accessory adhesion molecule to expedite colon epithelial cell–collagen interactions.[5] Because high concentrations of CEA are present in fetal tissue and tumors, it may disrupt the normally operative intercellular or cell–collagen adhesion forces allowing more cell movement and the development of a less ordered tissue architecture and greater cell–cell interaction.

The final application for measurement of circulating tumor markers and the area in which tumor markers appear to have the greatest clinical use is as a reflection of treatment efficacy and in follow-up for recurrent disease. In these settings, alterations in serum tumor marker levels may be the primary clinical variable influencing patient management decisions, such as continuing or discontinuing therapy or embarking on efforts to define the extent of disease by imaging studies or exploratory surgery. Unfortunately, even in the follow-up of patients with known diseases such as colon cancer, serum levels of CEA may not always reflect the presence or absence or extent of disease and so the surgeon cannot rely solely on these levels to make patient treatment decisions. In addition agents to treat colon cancer have not been very effective so that real elevations of serum levels of CEA have not necessitated changes in drugs or other agents because few, if any, effective agents are available.

Carcinoembryonic antigen and its use in the management of patients with colon cancer is an important topic for surgeons. Colon carcinoma is one of the most common and most lethal cancers. In 1989 approximately 150,000 Americans developed colorectal cancer and 60,000 died of the disease.[6] Effective, curative treatment of primary and even recurrent and/or metastatic colon cancer nearly always relies on surgical resection of all tumor mass. As mentioned CEA first was described 25 years ago and its

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use in management questions in patients with colon cancer has been studied fairly well. Unfortunately its current use is limited. In this issue of the *Annals of Surgery*, Yeatman and associates from the University of Florida suggest a new application of this marker that may improve its ability to detect liver metastases in patients with colorectal cancer.[7]

Recent studies indicate that new treatments may be effective in the management of patients with colorectal cancer. Postoperative radiation therapy and chemotherapy can prolong the disease-free interval[8] and subsequent survival[9] of patients with rectal adenocarcinoma who have undergone complete or curative surgical resection. Furthermore another recent study indicates that patients with Duke's stage C colon carcinoma (positive lymph nodes) have longer disease-free and overall survival intervals if treated with adjuvant fluorouracil (5-FU) and levamisole.[10] Finally highly meaningful improvements in objective response rates of patients with advanced unresectable colorectal cancer have been reported in six of seven recent trials with the use of 5-FU and folinic acid (either leucovorin or citrovorum factor) compared to 5-FU alone and in two of these studies an improvement in survival also was documented.[6] Therefore, despite the high incidence of colon cancer and its relatively poor prognosis, results of recent studies indicate new drugs that are active in the treatment of the disease and suggest that these agents may be useful in the management of patients with more extensive disease.

Occult, synchronous liver metastases are thought to be present in 10% to 30% of patients at the time of diagnosis of colorectal cancer. Because 25% to 30% of liver metastases from colon cancer may be, if detected early, resected for cure or treated with newer, potentially efficacious regimens such as 5-FU with leucovorin, a method to detect precisely liver metastases in patients with colorectal cancer would be very useful.[11] Preoperative imaging of patients with colorectal cancer using computed tomography (CT) and magnetic resonance has been limited in ability to detect and stage disease accurately.[12] With CT, staging accuracy rates as high as 90% have been reported; however other investigations demonstrate accuracy rates as low as 48%. Magnetic resonance imaging is similar, with accuracy rates of approximately 73%. In fact, even with the use of both imaging modalities, smaller, surgically curable lesions are more likely to be missed.[12] Presurgical staging with labeled antibodies to CEA and other markers also have been developed recently to stage patients with colon cancer. Indium-labeled monoclonal anti-CEA antibody imaging studies have been evaluated in patients with a history of colorectal cancer and elevated serum levels of CEA without detectable disease on standard imaging studies, including CT. In one recent study with 13 patients evaluated, anti-CEA imaging correctly detected recurrent tumor in 11, no recurrence in 1, and was incorrect in only 1 of 13 patients.[13] However that study had a large proportion of patients with local recurrences and only two patients had liver metastases.[13] Imaging with labeled antibodies to CEA has been less effective in localizing colorectal liver metastases, with a sensitivity rate of only 45% to 64%.[14,15]

Because accurate detection of liver metastases in patients with colorectal cancer remains a significant clinical problem, Yeatman and others have described a new method to detect the presence of liver metastases in patients with colorectal cancer. They have been able to measure elevated levels of CEA in the gall bladder bile of these patients (more than 10 ng/mL).[11] They reason that in the presence of CEA-secreting liver metastases, the concentrating ability of the gall bladder can concentrate CEA in the bile compared to serum levels. In this issue, they describe a perchloric acid extraction to remove the pigment and other bile proteins, allowing a simpler, more rapid radioimmunoassay with a lower detection limit.[5] Previously in *Annals of Surgery*, Yeatman et al.[11] described some important preliminary clinical investigations with this method. None of 7 patients with morbid obesity had elevated bile levels of CEA, and each of 17 patients with documented hepatic metastases from colorectal cancer had markedly elevated bile levels of CEA, while 2 of these patients had normal serum levels (100% sensitivity). Unfortunately there have been some false-positive results. Six of eight patients with either acute cholecystitis or cholangitis had elevated bile levels of CEA, and one patient with a primary hepatoma had markedly elevated bile levels of CEA. False-positive results in infections of the biliary tree may not be a problem because the presentation of patients with biliary infections is dramatically different from patients with colorectal cancer.

However the finding of marked elevations of gall bladder bile levels of CEA in a patient with hepatoma may diminish the usefulness of the study in cancer patients because the assay may not discriminate reliably between one type of liver cancer and another. Most worrisome was the finding that of seven patients with colorectal cancer without known liver metastases, three had elevated bile levels of CEA. This may represent a false-positive result because high venous effluent levels of CEA from the primary tumor entering the portal circulation. These high levels may bathe the liver and produce falsely high levels of CEA in the gall bladder bile. To rule out this explanation effectively, bile levels of CEA would have to be determined before and after the primary tumor had been removed. Another possible explanation is that occult, undetectable colorectal liver metastases are present but cannot be ascertained accurately with our current limitations of detection. The best plan to evaluate whether determination of CEA levels in gall bladder bile is helpful to diagnose occult, resectable and/or otherwise treatable liver metastases is a prospective study of serum and bile levels, at varying intervals in patients with primary colon cancer who are at risk of developing hepatic metastatic disease. Presumably gall bladder bile levels of CEA would have to be obtained by percutaneous transhepatic ultrasound or CT-guided repeated aspirations. Although this procedure can be performed safely, its invasive nature must be evaluated prospectively. It also must be determined whether it is cost-effective compared to determination of serum levels of CEA and repeated CT or magnetic resonance imaging studies. If ability to detect early lesions accurately can be corroborated, then subsequent studies may use gall bladder bile levels of CEA in these patients to alter treatment strategies: either exploratory surgery with ultrasound to assess and resect liver metastatic disease, or consideration of alternate therapy regimens. Portal vein infusional chemotherapy has been suggested by some,[16] and systemic chemotherapy with 5-FU and leucovorin has been suggested by others.[6] Treatment of tumor with yttrium-90–labeled monoclonal antibodies to CEA has prolonged survival markedly in experimental animal models of colon cancer that produce CEA.[17] In addition other recent studies make this approach more feasible in humans by using a second antibody to remove unbound circulating radiolabeled antibody, thus reducing the toxicity without influencing the anti-tumor effect.[18] Early definitive diagnosis of colorectal liver metastases by determination of elevated gall bladder bile levels of CEA may improve treatment efficacy and eliminate treatment failures in an organ in which most treatment failures occur.

Although the marker CEA first was described more than 25 years ago, new applications including measurement of levels in gall bladder bile,[7,11] anti-CEA antibody imaging[13–15] and treatment,[17,18] and new basic studies that demonstrate its cellular function[4,5] give it renewed emphasis and importance. These recent studies may appear promising but additional prospective, controlled studies will be necessary to determine the exact role of these potentially expensive and invasive procedures in the management of patients with colorectal cancer.

## References

1. Norton JA, Fraker DL. Malignant neoplasms: The role of specific serum tests in the diagnosis, management and evaluation of recurrence. *In* Sabiston DC Jr, ed. Textbook of Surgery, Update 2. Philadelphia: WB Saunders, 1989; pp 19–37.
2. Fletcher RH. Carcinoembryonic antigen. Ann Intern Med 1986; 104:66–73.
3. Jessup JM, Giavazzi R, Campbell D, et al. Growth potential of human colorectal carcinomas in nude mice: association with the preoperative serum concentration of carcinoembryonic antigen in patients. Cancer Res 1988; 48:1689–1692.
4. Benchimoi S, Fuks A, Jothy S, et al. Carcinoembryonic antigen, a human tumor marker, functions as an intercellular adhesion molecule. Cell 1989; 57:327–334.
5. Pignatelli M, Durbin H, Bodmer WF. Carcinoembryonic antigen functions as an accessory adhesion molecule mediating colon epithelial cell-collagen interactions. Proc Natl Acad Sci 1990; 87: 1541–1545.
6. Mayer RJ, O'Connell MJ, Tepper JE, Wolmark N. Status of adjuvant therapy for colorectal cancer. J Natl Cancer Inst 1989; 81:1359–1364.
7. Yeatman TJ, Kimura AK, Copeland EM, Bland KI. Rapid analysis of carcinoembryonic antigen levels in gallbladder bile: identification of patients for high risk for colorectal liver metastasis. Ann Surg 1990; 213:113–117.
8. Holyoke ED, Mittleman A, Panahon A, et al. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 1985; 312:1465–1472.
9. Douglass HO Jr, Moertel CG, Mayer RJ, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 1986; 315:1294–1295.
10. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; 322:352–358.
11. Yeatman TJ, Bland KI, Copeland EM, et al. Relationship between colorectal liver metastases and CEA levels in gallbladder bile. Ann Surg 1989; 210:505–512.
12. Moss AA. Imaging of colorectal carcinoma. Radiology 1989; 170: 308–310.
13. Doerr RJ, Abdel-Nabi H, Merchant B. Indium 111 ZCE-025 immunoscintigraphy in occult recurrent colorectal cancer with elevated carcinoembryonic antigen level. Arch Surg 1990; 125:226–229.
14. Beatty JD, Williams LE, Yamauchi D, et al. Presurgical imaging with indium-labelled anti-carcinoembryonic antigen for colon cancer staging. Cancer Res 1990; 50(Suppl):922s–926s.
15. Haller DG. Monoclonal antibody imaging in the management of patients with colorectal cancer. J Clin Oncol 1988; 6:1213–1215.
16. Taylor I, Machin D, Mullee M, et al. A randomized controlled trial of adjuvant portal vein cytotoxic perjusion in colorectal cancer. Br J Surg 1985; 72:359–363.
17. Hyams DM, Esteban JM, Beatty BG, et al. Prolongation of survival of nude mice bearing human colon cancer. Arch Surg 1989; 124: 175–179.
18. Blumenthal RD, Sharkey RM, Snyder D and Goldenberg DM. Reduction by anti-antibody administration of the radiotoxicity associated with $^{131}$I-labelled antibody to carcinoembryonic antigen in cancer radioimmunotherapy. J Natl Cancer Inst 1989; 81: 194–199.

# Splenic Trauma

## *Choice of Management*

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**The modern era for splenic surgery for injury began in 1892 when Riegner reported a splenectomy in a 14-year-old construction worker who fell from a height and presented with abdominal pain, distension, tachycardia, and oliguria. This report set the stage for routine splenectomy, which was performed for all splenic injury in the next two generations. Despite early reports by Pearce and by Morris and Bullock that splenectomy in animals caused impaired defenses against infection, little challenge to routine splenectomy was made until King and Schumacker in 1952 reported a syndrome of "overwhelming postsplenectomy infection" (OPSI). Many studies have since demonstrated the importance of the spleen in preventing infections, particularly from the encapsulated organisms. Overwhelming postsplenectomy infection occurs in about 0.6% of children and 0.3% of adults. Intraoperative splenic salvage has become more popular and can be achieved safely in most patients by delivering the spleen with the pancreas to the incision, carefully repairing the spleen under direct vision, and using the many adjuncts to suture repair, including hemostatic agents and splenic wrapping. Intraoperative splenic salvage is not indicated in patients actively bleeding from other organs or in the presence of alcoholic cirrhosis. The role of splenic replantation in those patients requiring operative splenectomy needs further study but may provide significant long-term splenic function. Although nonoperative splenic salvage was first suggested more than 100 years ago by Billroth, this modality did not become popular in children until the 1960s or in adults until the latter 1980s. Patients with intrasplenic hematomas or with splenic fractures that do not extend to the hilum as judged by computed tomography usually can be observed successfully without operative intervention and without blood transfusion. Nonoperative splenic salvage is less likely with fractures that involve the splenic hilum and with the severely shattered spleen; these patients usually are treated best by early operative intervention. Following splenectomy for injury, polyvalent pneumococcal vaccine decreases the likelihood of OPSI and should be used routinely. The role of prophylactic penicillin is uncertain but the use of antibiotics for minor infectious problems is indicated after splenectomy.**

### Historical Prospective

IN 1979 Roger Sherman detailed the most complete historical prospective of splenic injury.[1] From the mid 16th century through the end of the 19th century, there were several reports of 'splenectomy' that must challenge even the most credulous reviewers. The 1549 splenectomy by Zaccarelli on a 24-year-old woman with a progressively enlarging abdominal mass is thought by many to have been an oophorectomy.[2] Both of the reported 17th century 'splenectomies' were performed for an eviscerated spleen that protruded through a penetrating anterior abdominal stab wound in one patient and through a left flank stab wound in the second patient. The spleen protruding through the left flank wound first was devascularized by ligation of the exposed pedicle and then resected 3 days later.[1] All four of the reported 18th century 'splenectomies' for trauma were performed for injured spleens that eviscerated through similar penetrating abdominal wounds. At least three of these four resections were 'partial splenectomies' of that portion of spleen that was exposed while the remaining spleen was left alone. The circumstances of the first 'splenectomy' for trauma in the United States, in 1816, are similar; the spleen eviscerated after a knife was withdrawn from the abdomen and successful removal was accomplished by ligation of the vascular pedicle and detachment of the distal part.[3] Most 19th century reports of splenectomy were accomplished with the same facility because the eviscerated spleen was excised without open celiotomy. Oh that the glories of surgery could be achieved with so little effort!

How can a penetrating object simultaneously detach retroperitoneal splenic attachments, mobilize the distal pancreas, reflect the splenic flexure of the colon, and stretch the splenic artery and vein to permit spontaneous extrusion of the spleen through the abdominal wall defect

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once the wounding agent has been removed? After treating thousands of patients with penetrating abdominal wounds and hundreds of patients for splenic injury, I have yet to see an eviscerated spleen. When questioned about this curiosity, none of our regional trauma surgeons have witnessed this wondrous event. Personal querying of individual surgeons representing most of the major urban trauma centers in the United States yielded not a single patient presenting with a penetrating wound filled with an extra-abdominal spleen that could be excised without celiotomy.

Following penetrating wounds, evisceration of the small bowel is a frequent occurrence. Certainly our forebears would have recognized the difference between the small intestine and the spleen; lack of recognition followed by partial or total excision of the eviscerated organ without anastomosis would certainly have led to a fatal conclusion. Colon evisceration is less frequent and may, if bloodied and edematous, be difficult to recognize; partial or total excision without anastomosis, however, would lead to the same fatal outcome. The most common organ eviscerating through a penetrating wound is the omentum. Although the eviscerated omentum usually can be recognized, the presence of blood and blood clot within the leafs and venous congestion with edema due to obstruction of venous return at the site of evisceration sometimes causes the omentum to appear as a solid organ. This extruded mass may enlarge from the combination of venous congestion and contained expanding hematoma to the point where it may actually appear like a spleen. The congestion and swelling preclude return of the swollen omentum to the peritoneal cavity, as has been described in several of the above reports. Furthermore the swollen congested hemorrhagic omentum thins out at the point of exit from the peritoneal cavity, thus, appearing as a 'pedicle,' which could be easily ligated before removal of the extra-abdominal mass. The ligated pedicle, in the 20th century, is returned to the peritoneal cavity, after which a formal laparotomy is performed. The author suspects that the only difference between this 20th century description of preceliotomy omentectomy and the earlier reports of 'splenectomy' is that our forebears did not perform the formal laparotomy, which would have demonstrated an uninjured spleen in its normal anatomic location. Consequently one must view any perceived relationship between these historical 'splenectomies' and subsequent infectious complications as being spurious and completely unrelated to an asplenic state.

The modern era of splenic surgery for trauma began in 1892 when Riegner reported the first successful splenectomy for blunt injury.[4] His patient was a 14-year-old construction worker who fell from a height and hit his abdomen. He presented with the combination of abdominal pain, abdominal distension, tachycardia, and oliguria. Through a large abdominal incision, Riegner performed total splenectomy for a badly shattered spleen, part of which was lying free in the peritoneal cavity. Two major milestones were established by this procedure. First the advantage of definitive laparotomy rather than abdominal compression for refractory intra-abdominal bleeding was reinforced by the successful outcome. Second the successful outcome helped establish the role of splenectomy as a safe and effective procedure for refractory intra-abdominal bleeding. This success also helped lay to rest the 19th century concept that the spleen was necessary for life.

## Splenic Function

Throughout the centuries, splenic worth has vacillated from the lofty pedicle of an essential organ for life to the lowly depths of a vestigial organ without merit. More than 2000 years ago, Aristotle suggested that the spleen had no purpose.[5] Pliny, the first-century historian, proposed that the congested spleen hinders runners.[1] Modern anatomists might wonder how Pliny knew of the spleen, let alone that it had the potential for congestion. Pliny added that the asplenic state might cause loss of humor or laughter; one can only be intrigued by the data base that led to this conclusion. The concept that the spleen produces laughter was perpetuated through the 16th century in the Babylonian Talmud.[1] Later Maimonides postulated that the spleen was responsible for the purification of blood and not laughter; presumably impure blood hinders laughter.[6] In the many years that followed, the spleen escalated in status and, by the 17th century, was considered essential for the maintenance of life. This lofty position eroded gradually as new data emerged. Malpighi performed ligation on the splenic artery in dogs who had no untoward effects; this helped demonstrate that the avascular spleen could also sustain life.[7] During the next 100 years, splenectomy was accomplished in several animal species, all of which survived the asplenic state. Pearce,[8] in 1918, reported that 25% of animals subjected to splenectomy die from peritonitis or pneumonia. He thought these deaths were unrelated to the asplenic state because he concluded that the animal survives without the spleen with 'relative impunity.' He did note, however, that the hematologic changes following splenectomy included anemia, eosinophilia, and leukocytosis, all of which were of unknown significance.

Despite this review by Pearce, little attention was directed toward the role of the spleen in the defense against infection. Morris and Bullock,[9] in 1919, were the first to document, in a controlled scientific model, the importance of the spleen in defense against infection. These authors performed splenectomy in rats that were then subjected to a Pasteurella bacterial challenge and compared to well-established responses in control eusplenic rats. These authors concluded that the spleen in rats helps fight infection and that the removal of the spleen eliminates this defensive mechanism. These authors further expressed a concern that humans who survive splenectomy may be unable to resist a subsequent infectious insult. Their warning is precise and prophetic, stating that is was probable '. . . that the human body deprived of its' spleen would show . . . increased susceptibility to infection and some of the fatalities . . . attributed to infection . . . may be due to splenectomy.'[9]

Despite these early warnings, the surgical community moved down a road of wonting splenectomy with little or no regard for splenic salvage. Many surgical leaders, including Bailey, Moynihan, and others reported on small numbers of patients with poor follow-up and concluded that the fears of increased susceptibility to infection after splenectomy were unfounded.[1,10,11] Despite the pleas by Pfeiffer,[12] in 1924, for a more careful follow-up of these patients, the same teachings persisted and the controversy disappeared for a generation. Possibly the golden era for the evolution of individual surgical giants squelched minority views, including those regarding the potential importance of splenic salvage.

Thirty years later King and Shumacker[13] revived the controversy when they reported on five children who developed severe overwhelming infection after splenectomy for congenital spherocytosis.[13] Two of these five children rapidly died from the syndrome, which has since been named overwhelming post splenectomy infection (OPSI). Stimulated by this report, other authors identified OPSI following splenectomy performed in children for other hematologic disorders.[14,15] Initially the occurrence of OPSI after trauma was not appreciated so that the infectious sequelae in these children were thought to result from the underlying disease process rather than the asplenic state.[14-16] In 1957 Smith[17] made the first report of OPSI following splenectomy for trauma. This milestone report stimulated other centers to identify the same phenomenon in injured patients so that, by 1970, most centers recognized OPSI following splenectomy for trauma in children. Consequently discussion of splenic function and infection in children led to the concept that the immune system was immature in children.

The spleen, at birth, is considered functionally and histologically immature.[18,19] The neonatal spleen has few lymphoid follicles and little or no germ centers. This raises questions about the humoral capabilities of the young spleen in response to antigenic stimulation. By puberty the spleen increases to its maximal weight and represents approximately 25% of the total-body lymphoid mass. Does this increase in size represent the full humoral capacity of the spleen or is this simply the lymphoid mass response to many different antigenic stimuli received during this phase of maturation? The splenic blood flow by puberty and in the adult is generous, averaging 25 mL per minute. This splenic blood flow, presumably, facilitates leukocyte sequestration and the production of immunoglobulins and antibodies to circulating antigens. The efficacy of splenic function is tested partially by the ability to clear particulate materials or bacteria from the blood stream. Because a portion of this clearance may be related to splenic filtration, maintenance of generous splenic blood flow and splenic mass appear necessary to sustain this function.[19,20] Several studies show that splenectomy reduces intravascular clearance of particulate matter, including antigens. This impairment can be correlated with decreased opsonic factor synthesis and decreased release of antibodies in response to specific antigen stimulation.[21] One opsonic factor is tuftsin, a peptide that is cleaved from the gamma globulin molecule, leukokinen, by a polymorphonuclearcyte (PMN)-containing enzyme. The product of this intrasplenic cleavage circulates and, when acting in concert with PMNs, enhances opsonization and phagocytosis of bacteria.[21] The asplenic state leads to a decrease in tuftsin and immunoglobulins so that their defense activities have disappeared by 8 weeks. This includes impaired alveolar macrophage phagocytosis and depressed T-cell (T-helper) activity. The greatest reduction in bacterial clearance is seen with the encapsulated gram-positive bacteria. The efficacy of bacterial clearance is proportional to splenic mass, thus making a further case for partial splenic salvage.[20] Reduced bacterial clearance, however, is not limited to the gram-positive encapsulated organisms. Ohshio and coworkers demonstrated a postsplenectomy decrease in IgG anti-lipopolysaccharide antibody complex when mice were immunized on postsplenectomy days 1, 3, and 7 as compared to mice undergoing sham laparotomy without splenectomy.[22]

The impaired immune response after splenectomy is not limited to intravascular phenomena. Because pneumococcus is an air-borne bacterium, the respiratory route of entry also has been studied. Indeed the lungs are probably the source of OPSI in some patients.[23,24] In 1989 Hebert[23] showed that splenectomy in mice leads to decreased bacterial clearance from the lungs after an aerosol challenge of known quantities of streptococcus pneumoniae type III given 2 weeks after operation. Reduced clearance in this model is associated with altered translocation of bacteria from the tracheobronchial air passages to regional lymph nodes where antimicrobial activity occurs.[25] The complexity of these interwoven but cryptic defense activities is enormous and probably involves altered phagocytosis and reduced PMN efficacy. Among many other functions, this impaired defense against an aerosol bacterial challenge is lethal and can be ameliorated by partial splenic salvage.[23,25] Mice with 50% splenectomy and 25% splenectomy had, proportionally, better clearance and better survival. The decreased clearance of particulate matter coincides with impaired ability to clear *Escherichia coli.*

The intact spleen also is important for a normal response to vaccination with polyvalent pneumococcal vaccine. Ohshio[22] showed that preoperative immunization would not prevent a decrease in antibody response when splenectomized mice were challenged 30 days after splenectomy with the same antigen. They concluded that the intact spleen is necessary to mount a recall response of the anti-lipopolysaccharide antibody complex to a postoperative antigenic stimulation. Hosea[26] and coworkers also demonstrated an impaired antibody response to pneumococcal vaccine after splenectomy. Rabbit studies demonstrated reticuloendothelial system failure to clear particulate material from the blood stream following splenectomy. This reticuloendothelial system failure was associated with a decrease in plasma fibronectin levels with or without the added insult of sepsis that was established by open appendectomy without ligature.[26]

This impaired immunologic response contributes to the development of OPSI. This syndrome is now well established in children, with an incidence about 0.5%. The clinical features are dramatic and suggest a bacteremic shower.[1,17,18] This produces constitutional symptoms that are multisystem and devastating. The gastrointestinal symptoms include nausea, vomiting, and diarrhea. The general cardiovascular symptoms include overwhelming weakness, progressing to a prostrate state. Worsening headache is associated with increasing fever leading to coma. This overwhelming syndrome may progress from onset to death within 24 hours. Late cardiovascular collapse is associated with a rising pulse rate and hypotension. Varied electrolyte abnormalities may be encountered and these include hypoglycemia, despite glucose administration and hyponatremia mimicking adrenal insufficiency. Indeed some patients have adrenal changes on postmortem examination.

The organisms responsible for OPSI include pneumococcus, which occurs in at least 50% of patients, meningococcus, *E. coli*, *Haemophilus influenza*, Staphylococcus, and Streptococcus.[27] The clinical syndrome suggesting a bacteremic shower is reinforced by the frequent identification of many bacteria on culture and sensitivity studies and the occasional bacterium seen on a peripheral blood smear. Antibiotics, even when administered early, may fail to avert the progressive nature of this syndrome, which has a mortality rate of more than 50%.

This syndrome of OPSI probably occurs also in adults.[28] I became convinced of OPSI in adults in 1977 when a former student, now an infectious disease expert, detailed the successful treatment of OPSI in a healthy 29-year-old adult 6 years after splenectomy for blunt trauma. This patient almost died from meningococcus meningitis and pneumonitis. After splenectomy, I gave the patient neither polyvalent vaccine nor advised the patient about increased risk for subsequent OPSI and the importance of early antibiotic therapy for subsequent infections. Despite similar anecdotal examples by other surgeons, the surgical community is still slow to accept OPSI in the adult population. I recall vividly the verbal abuse from a well-known fellow panel member in 1979 after encouraging enhanced efforts at splenic salvage to preclude the risk of OPSI in adult patients. Fortunately the pendulum has swung toward splenic salvage in adult patients during the past decade.

## Splenic Salvage

### *Operative*

The story of splenic salvage in Western medicine is not exemplary. Despite frequent anecdotal reports on the feasibility of splenic salvage and the late risks of splenectomy, the routine for splenic injury remained total splenectomy. In 1897 Zikoff[18] may have performed the first splenorrhaphy for trauma. In the next generation, isolated reports of splenorrhaphy appeared but received little attention. Dretzka, the first Chief of Surgery at Detroit Receiving Hospital, reported the first splenorrhaphy in a child.[1,18] This report, in 1930, clearly outlines the technical considerations necessary for successful repair. A generous incision permits full exposure to the left upper quadrant contents. When splenic bleeding is contained by a pack, the surgeon may divide the greater omentum outside the gastroepiploic vessels, mobilize the splenic flexure of the colon inferiorly, and retract the greater curvature of the stomach anteriorly and inferiorly to identify and divide the short gastric vessels. The retroperitoneal and diaphragmatic splenic attachments can then be divided as the plane between the posterior surface of the spleen with pancreas and the retroperitoneal tissue can be dissected. The surgeon must resist the temptation to pull the partially mobilized spleen into the abdominal incision. The younger surgeon must be taught to push the pancreas anteriorly and medially, thus allowing the spleen, by necessity, to come along for the ride. Once fully delivered to the incision, attention can be directed toward the technical nuances of splenic salvage. When the spleen is bleeding actively, the surgeon may forgo complete division of all attachments before mobilization. When rapid mobilization is necessary, the potential for irreparable iatrogenic trauma in enhanced, as is the likelihood for total splenectomy. Once completely mobilized, the techniques for splenorrhaphy are similar to those used for hepatorrhaphy, but the spleen must be handled more gently. Morgenstern[29] has highlighted these technical features. Most authors prefer the use of absorbable sutures to obtain splenic hemostasis.[29-33] Gently placed simple or figure-eight sutures

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of 3/0 absorbable suture permits sufficient compression of the splenic parenchyma to obtain hemostasis in most instances (Fig. 1). The need for gentleness cannot be over emphasized. When two sutures are placed in close proximity, one suture may be held at the desired tension while the second suture is tied precisely. This circumvents inadvertent parenchyma tearing. The intraparenchyma splenic vessels course both parallel and perpendicular to the hilar vessels and can be controlled with fine crisscrossing sutures using, in the authors hands, 4/0 silk (Fig. 2). Bleeding from needle holes should be contained by gentle pressure for 5 to 10 minutes or the application of a pack over the splenic repair as the spleen is returned to the left upper quadrant. The pack, when kept opposed to the splenorrhaphy site while the surgeon corrects problems elsewhere, completes the hemostasis. Once good hemostasis is achieved, the spleen should no longer be mobilized.

When the spleen is too badly injured for simple splenorrhaphy, splenic salvage may be achieved by partial splenectomy, remembering that the amount of preserved splenic mass correlates with maintained resistance against infection (Fig. 2). During partial splenectomy, the intraparenchymal vessels and the margin of resection are repaired by the techniques outlined above. Preserving intact capsular coverage of resected margins with denuded parenchyma facilitates hemostasis. Hilar vessels supplying the resected portion can be clipped or tied, with the surgeon being careful to avoid injury to those hilar vessels feeding the remaining spleen. The severely pulverized segment of spleen is best treated by resectional debridement back to an area of reasonably normal splenic substance that will hold sutures.[29-33]

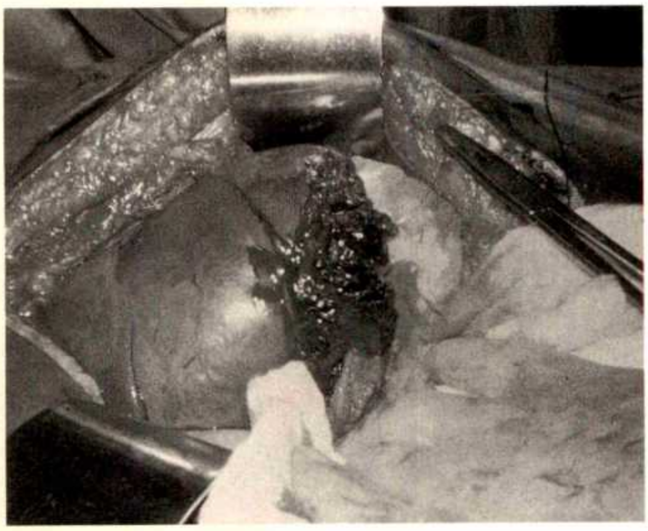

FIG. 1. After full mobilization, carefully placed and gently tied 3/0 absorbable suture splenorrhaphy provides good hemostasis in most type II splenic injuries without hilar vessel injury.

Besides splenic suture and direct pressure, several other techniques have been promulgated for intraoperative splenic salvage (Fig. 3). Electrocautery is very beneficial for minor oozing from denuded parenchyma, the splenic capsule, and small intraparenchymal vessels.[32] The ultrasonic surgical aspirator has been described for partial splenectomy.[34] Hemostatic agents containing a mixture of fibrinogen, thrombin, and collagen have been applied successfully to splenic injuries topically (Fig. 4).[35] Polyglycolic acid mesh can be wrapped around the badly injured spleen and then sewed to itself to maintain the splenic substance within its normal anatomic confines.[36] Delany[37] and coworkers wrap and suture this mesh to the badly injured spleen. The laser has been used for splenic salvage in dog studies.[28] Rabo and Ger[38] proposed stapling for splenorrhaphy. Using 4.8 mL and 3.5 mL staples, these authors perfected the technique in canine studies before successful clinical application. Despite the plethora of ancillary techniques used to augment the surgeon with splenic salvage, none of these techniques will replace good, careful, gentle surgical technique and mature surgical judgment.[35]

Using these techniques, the success rate of operative splenic salvage is quite good. Surgical teams, dedicated to operative splenic salvage in the adult patient, will achieve success in at least 50% of patients after both blunt and penetrating injury.[30-33] Moore and coworkers[32] achieved splenic salvage in 85 of 170 patients. The best success was achieved in those patients who required hemostasis by either electrocautery or the local application of topical hemostatic agents; these patients had lesser injuries and none required reoperation. The need for sutures or debridement for hemostasis was associated with a 2.5% incidence of postoperative rebleeding requiring reoperation. The patients with more severe splenic injury requiring a partial splenectomy had a 10% incidence of significant rebleeding requiring reoperation. Feliciano and coworkers[31] reported a similar success with operative splenic salvage. The national incidence of operative splenic salvage will depend on the emphasis and dedication by each surgical group. Consequently the success rate of splenic salvage varies from as low as 5% in adults to as high as 85% in children.

Splenic salvage has spread into the arena of surgery for pancreatic injury.[32] Those patients with type II pancreatic injury thought to involve the main pancreatic duct in the body or tail of the pancreas traditionally have been treated by a distal pancreatectomy with splenectomy. This operation can be performed without splenectomy.[32] Careful mobilization of the pancreas near the site of injury permits identification of the splenic artery and vein, which are ligated and divided as the pancreas is transected. The pancreas then is mobilized toward the spleen, with the surgeon being careful to identify individually the terminal branches of the splenic artery and vein to achieve he-

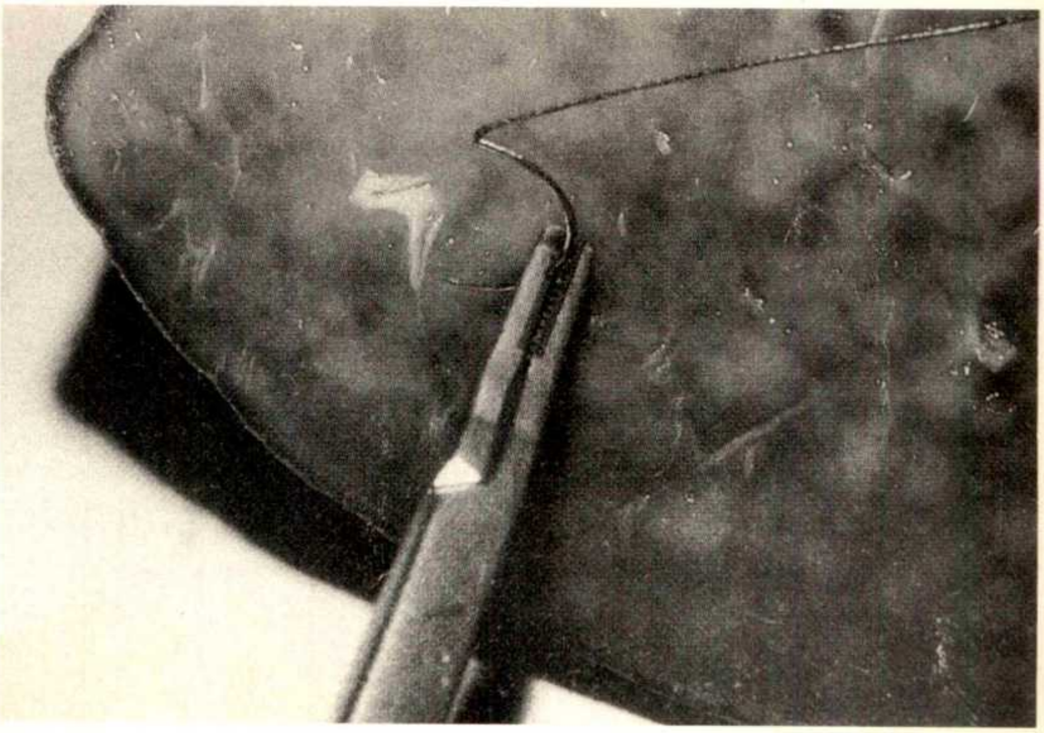

FIG. 2. Intraparenchyma vessel sutured with fine silk criss-cross suture technique provides good hemostasis to most hilar vessels.

mostasis within the splenic hilum. When feasible, the splenic artery may be preserved. The retroperitoneal and diaphragmatic attachments of the spleen are left intact, as are the short gastric vessels. The extra time needed for this operation would be unwarranted in a patient with active bleeding when pancreatectomy with splenectomy is the quickest technique for rapid hemostasis. This approach to the pancreas also can be applied to patients with combined pancreatic and splenic injury when the splenic injury is minor and can be made hemostatic by means of electrocoagulation or the topical application of hemostatic agents without requiring full mobilization from the adjacent tissues.

Some patients require splenectomy.[39] The class IV

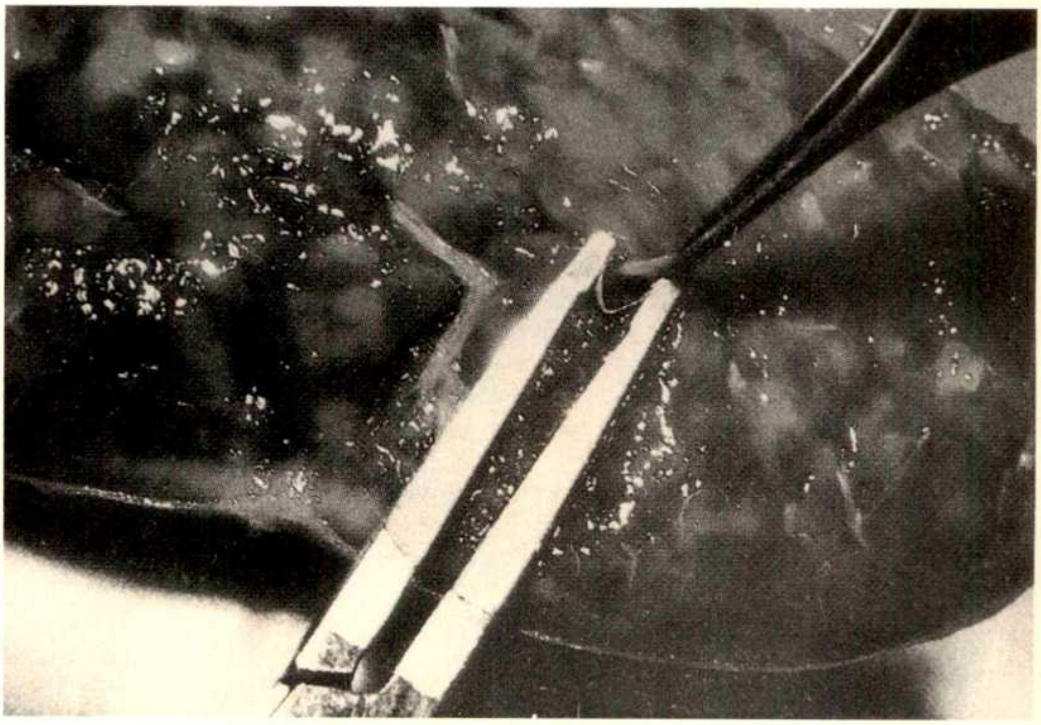

FIG. 3. Hilar vessels near hemisplenectomy margin are held by fine, smooth pick-ups before occlusion by silver clip.

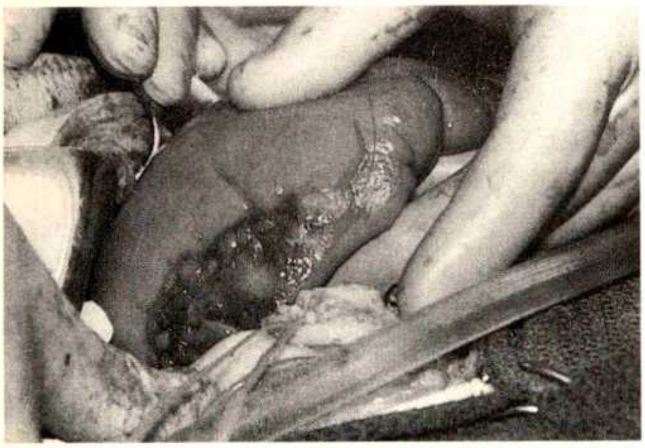

FIG. 4. Topical hemostatic agent is applied to hemisplenectomy margin to contain oozing.

splenic injuries with shattered, torn parenchyma or avulsed segments of crushed parenchyma rarely are salvaged. Patients with portal hypertension and increased bleeding from all splenic attachments uniformly require splenectomy. Patients with associated splenic disease, such as splenitis, infectious mononucleosis, malaria, lymphoma, or other intrinsic abnormalities seldom have successful splenic salvage. Finally the extra time required for splenic salvage in patients with active bleeding from the spleen and elsewhere is unwarranted. The mature surgeon intuitively recognizes when the threat of immediate hemorrhage outweighs the threat of remote OPSI. Even after splenectomy, splenic function may be preserved by autotransplantation.[32] This is accomplished by cutting the excised spleen into small fragments measuring no more than 2 mm in largest dimension. These multiple, small fragments representing at least 50% of spleen mass are placed within omental pockets as the omentum is folded on itself and held in position with through-and-through absorbable sutures. The end product looks like a splenic omelet. Moore and coworkers[32] reported on 43 patients treated by immediate replantation.

The natural history of the splenic replanted tissue includes early extensive coagulative necrosis followed by later regeneration with the ultimate return of splenic function being delayed for 5 weeks to 6 months.[40] In 1988 Rhodes and coworkers[40] described a patient who developed an omental abscess following the splenic omelet procedure after a distal pancreatectomy and splenectomy for pancreatic pseudocyst. The patient was returned to the operating room on day 11, at which time the abscessed omentum with replant was excised and the patient recovered. He suggested that the period of coagulative necrosis may be a time for increased susceptibility to infection and that this procedure should be avoided in any patient with peritoneal soilage or with the potential for subsequent sepsis from associated conditions. Following splenectomy and splenic replantation, the author observed an unusual infectiouslike response. A 56-year-old woman did well during the first postoperative week, although adynamic ileus delayed the onset of oral nutrition. This resolved and the patient was about to go home on day 8 when she became febrile (temperature, 104°F), very ill, and jaundiced (bilirubin level, 13.7 mg/dL). She was restarted on intravenous fluids with antibiotics and slowly recovered over the next 7 days and was discharged. The reason for this bizarre response remains cryptic as it was too severe for an infectious process, which never pointed, and too early for a blood transfusion reaction. We attribute this response to the systemic and hepatic effects of necrosis and lysis of the replanted spleen fragments. These anecdotal observations may mirror the 10% incidence of multiple-organ failure or sepsis reported by Moore and coworkers.[32] Possibly the loss of splenic blood filtration during the early postreplantation interval precludes normal splenic defense function, whereas necrotic splenic fragments may be an attractive source of nourishment for bacteria. Much work in the animal laboratory needs to be done before widespread replantation becomes routine.

### *Nonoperative*

More than 100 years ago, Billroth suggested that the injured spleen has the ability to heal itself.[1] He described the autopsy findings of a 43-year-old patient who fell at work, sustaining both head and abdominal injuries. The patient died 5 days later and the postmortem examination showed a splenic injury with no evidence of recent bleeding. Billroth observed 'from the appearance of the *rent*, and the small quantity of blood effused, we concluded that this injury might have healed up completely.' This farsighted view received little attention because the surgical community was not ready for the nonoperative therapy of splenic injury. The concept of nonoperative treatment was delayed further when the specter of delayed splenic rupture was raised. In 1932 MacIndoe[41] reported that secondary hemorrhage from splenic injury occurs frequently and has a mortality rate comparable to that seen with primary splenic rupture. Based on this statement reflecting treatment of a single patient, a concept evolved that delayed splenic rupture occurs with 10% to 15% of splenic injuries. Because diagnostic peritoneal lavage and abdominal computed tomography (CT) scans have been used for blunt abdominal trauma, the incidence of delayed splenic rupture is less than 1%. The concept that an intrasplenic hematoma would expand and rupture several days or even weeks after injury because the lysed red cells caused a slowly expanding hyperosmolar cavity is now recognized as a product of inadequate diagnostic tests. I have seen only one patient with a negative (crystal clear) peritoneal lavage effluent followed later with intraperitoneal hemorrhage from a ruptured splenic hematoma.

Concerned about the splenic protective role against infection, Wanborough is reported to have initiated nonoperative therapy for suspected splenic injury at the Sick Children's Hospital of Toronto in the 1940s.[1] Any logical discussion of nonoperative splenic salvage necessitates a review of the initial diagnostic measures used in the acutely injured patient.[42] Controversies regarding initial diagnosis and management include (1) routine exploration *versus* observation for stab wounds, (2) the value of techniques used to define peritoneal penetration, (3) the role of exploration for penetrating gunshot wounds, (4) the value of diagnostic paracentesis (DPC) or diagnostic peritoneal lavage (DPL) for penetrating wounds, and (5) the value of DPL *versus* abdominal CT scan after blunt injury. Recognizing the many diverse views regarding these issues, the following recommendations incorporate some degree of author bias.

When the clinical workup suggests ongoing bleeding of suspected intra-abdominal origin after either blunt or penetrating injury, immediate operative intervention is mandated. Following successful hemostasis, diagnosis and therapy for other injuries can be completed in the operating room. When some doubt exists about the site of massive bleeding, partial resolution can be provided immediately by DPC performed on the lateral border of each rectus muscle at the level of the umbilicus. If this 20-second test yields no blood, the surgeon should reflect a moment before opening the abdomen to control massive hemorrhage. The more sensitive but more time consuming DPL probably will confirm that the cause of unstable vital signs lies outside the peritoneal cavity. If the effluent from DPL contains less than 100,000 red cells/mm$^3$, has a hematocrit level less than 1%, or permits the reading of news print through standard diameter intravenous tubing, then massive hemoperitoneum is absent.

The approach to penetrating stab wounds varies among surgeons. Those who adhere to the rule that all penetrating stab wounds require exploratory laparotomy try to identify when a wound has penetrated to reduce the incidence of negative laparotomies. Techniques popularized for confirming penetration include simple digital examination with the gloved finger, sinography through the stab wound, local exploration of the stab wound to its deepest level or to the peritoneum, and DPL assuming lack of penetration when the effluent is clear. Those who prefer selective observation of patients with penetrating stab wounds rely solely on the physical findings. Thus patients with stable vital signs and no peritoneal irritation are observed. When such a patient develops a decrease in hemoglobin without pain or tenderness, abdominal CT scan is performed in search of a splenic or liver injury.

When a patient presents with a stab wound along the left lower rib cage causing hemothorax, perforation of the left hemidiaphragm may result without any signs or symptoms. Diagnostic peritoneal lavage in this instance should be considered positive when any amount of blood is returned with the effluent because the patient probably has penetration of the diaphragm. Exploratory laparotomy and repair of the diaphragmatic injury prevents the subsequent development of a diaphragmatic hernia and permits the identification of associated splenic or hollow viscus injury. When a parasplenic hematoma is left unrecognized, the patient may return after chest tube removal with left upper quadrant fullness and medial deviation of the stomach on plain abdominal films or upper gastrointestinal series (Fig. 5). Once laparotomy is performed for the left upper quadrant mass, the diagnosis of splenic injury with parasplenic hematoma is confirmed. Splenic salvage at this time often is not successful.

When a patient presents with a penetrating gunshot wound, laparotomy is recommended. When question exists about penetration of the peritoneal cavity, DPL showing any blood in the effluent confirms penetration. A negative DPL in a patient with an abdominal gunshot wound, unfortunately, may be associated with a retroperitoneal injury. Thus any patient with positive abdominal signs or symptoms needs laparotomy, at which time an injured spleen will be identified. Therefore there is no literature on the natural history of a spleen being observed following a gunshot wound. As more surgeons observe patients with left thoracic gunshot wounds with positive double-contrast

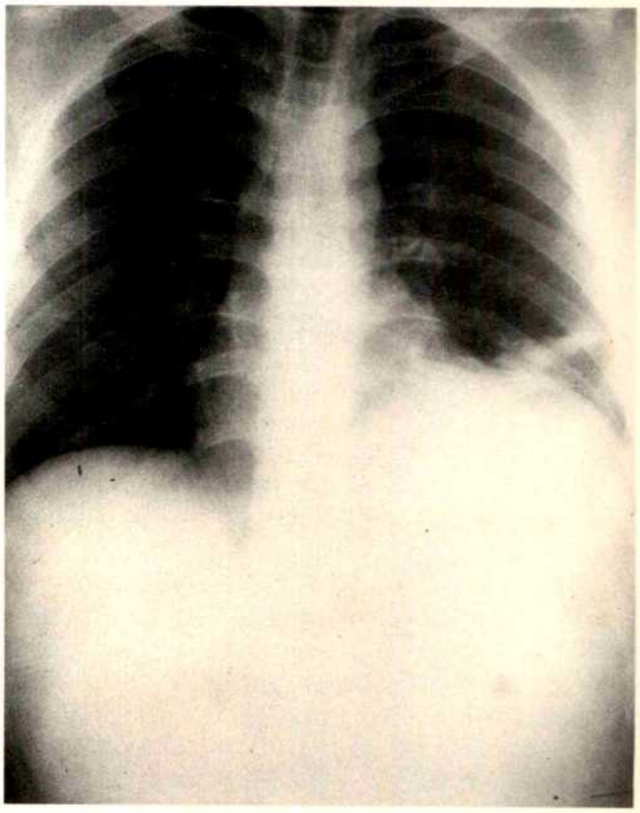

FIG. 5. Following successful tube thoracostomy therapy for a left hemothorax from a gunshot wound, this patient returned 10 days later with elevation of the left hemidiaphragm due to a ruptured spleen. Initial DPL showing small amount of bloody effluent would have confirmed diaphragmatic perforation.

abdominal CT scans, the natural history may emerge. A patient with a left lower thoracic wound with hemothorax and perisplenic blood on abdominal CT scan, despite the absence of positive physical findings, has a splenic injury. If this is observed, the natural history will be defined.

Much controversy revolves around the relative merits of abdominal CT scan *versus* DPL after blunt injury. Rather than being in competition, these two examinations are complimentary, with each having specific objectives.[42] When the patient presents with stable vital signs, a DPL, when negative, rules out hemoperitoneum. When DPL is positive, hemoperitoneum is confirmed and a judgment must be made about the presence or absence of hollow viscus injury. An elevated white cell count, high amylase content, or the presence of particulate matter or bacteria within the lavage effluent indicate hollow viscus perforation. If no obvious intraperitoneal hollow viscus injury exists, assessment is made for possible injury to the retroperitoneal organs, particularly the pancreas, duodenum, and genitourinary system. An abdominal CT scan with double contrast, including intravenous and oral contrast, provides excellent assessment of these organs. Sorkey and coworkers[42] emphasize that DPL and the double-contrast abdominal CT scan should be used in a complimentary manner to aid diagnosis and guide therapy.

Serial clinical examination of the stable patient with blunt injury frequently may lead to false-positive and false-negative conclusions. The error rate is magnified in patients with compromised mental function. The resultant delay in diagnosis and operative intervention reduces the likelihood for splenic salvage. Whenever blunt abdominal trauma occurs in association with alcohol ingestion, recent drug usage, schizophrenia or other psychic abnormality, mental retardation, or associated head injury, DPL or abdominal CT scan are essential.[42] When mental functions are uncompromised and serial abdominal exams are absolutely normal, the patient will be discharged if no other reasons for admission exit. If this patient requires operative intervention for associated injuries, DPL is indicated to circumvent the risk of unsuspected intraperitoneal bleeding during anesthesia. If this patient has hematuria, an elevated serum amylase level or abnormal abdominal x-rays, a double-contrast abdominal CT scan is needed before operation. When clinical examination and DPL are negative, a class I splenic injury, namely, a subcapsular hematoma, may go unrecognized and not appear on the list of patients with successful splenic salvage.[43]

When abdominal findings are equivocal or the hemoglobin level declines inappropriately, DPL is recommended. When DPL in a stable patient is positive for blood but negative for white cells, amylase, particulate matter, and bowel content, abdominal CT scan is warranted. When the DPL is positive for amylase, particulate matter, white cells, or bowel content, laparotomy is mandated. Whenever a patient being examined by abdominal CT develops symptoms of peritoneal tenderness or becomes unstable, immediate resuscitation and cancellation of the examination in favor of immediate operation is mandatory. Successful surgical intervention of stable patients with potentially lethal injuries is highly successful; surgical intervention of unstable patients compromises this surgical success. Thus the unstable patient should never have abdominal CT scan.

The success of nonoperative treatment of splenic injury in children has been so successful that many pediatric surgeons have abandoned DPL in favor of abdominal CT scan.[30] This approach may be, in part, motivated by the desire to avoid unnecessary laparotomy in children with positive DPL. Rather than discarding a good test such as DPL, the pediatric surgeon might modify the criteria for laparotomy based on DPL findings. When the child has a positive DPL for blood only, he or she could be watched using the same criteria for those diagnosed to have splenic injury on the CT scan. A negative DPL would, in many patients, preclude the need for an abdominal CT scan, whereas a DPL positive for bowel content or amylase would direct early operative intervention when associated splenic injury would be identified and salvaged. The disadvantage of early DPL is that not all the lavage infusate exits by gravity, so a portion of the intraperitoneal fluid seen on subsequent CT scan would be electrolyte solution and not blood. This factor should not interfere with successful nonoperative management of splenic injury. The earlier diagnosis of intraperitoneal hollow viscus injury by DPL may become more relevant with increased compliance with new laws regarding automobile back seat restraints. The incidence of hollow viscus injury in children is higher with the back seat lap restraints and these injuries are not diagnosed best by abdominal CT scan.[44]

Although calculated observation of suspected splenic injury was practiced sporadically during the 1960s, this mode of therapy was unpopular in adults until the 1980s. Most surgical teams observing suspected splenic injury in the 1970s based the diagnosis on liver-spleen radionuclide scans or arteriography. Both exams have a significant false-positive rate when compared with computed tomography.[45] Consequently one may question the published success rate of nonoperative splenic salvage in the 1970s. During the 1980s, computed tomography became established as the standard for diagnosis of splenic injury.

Even the CT scan has limitations. Buntain and Gould identified two patients with unrecognized intrasplenic hematoma diagnosed during operation performed for other reasons.[30,43] These authors offered an excellent classification of splenic injury (Table 1). Class I injuries include subcapsular or intraparenchymal hematomas without capsular disruption or parasplenic blood. Class II injuries include open tears or fractures that involve the parenchyma but do not extend into the splenic hilum. These patients have free intraperitoneal blood, which may spread

TABLE 1. *Severity of Splenic Injury*

| Type | Signs |
|---|---|
| Type I | Subcapsular or intraparenchymal hematomas without capsular disruption |
| Type II | Open parenchymal tears or fractures that do not extend into the hilum |
| Type III | Large open fractures extending into the hilum |
| Type IV | Shattered or pulpified spleen with hilar disruption or avulsed fragments |

beyond the left upper quadrant. Class III injuries extend into the hilar structures and cause more hemoperitoneum. Class IV injuries include the shattered or pulpified spleen, which may be avulsed partially from its hilar attachments. Based on CT, these authors further subdivided splenic injuries according to associated organ injuries, with subtype A patients having no extrasplenic injuries, type $B_1$ patients having associated solid viscus injury, and type $B_2$ patients having associated hollow viscus injury. Buntain and associates[43] reported that the class of splenic injury correlated significantly with the injury severity score but not with the trauma score. Successful nonoperative therapy was achieved in all class I injuries, 60% of class II injuries, 7% of class III injuries, and none of the class IV injuries. Rescinitti[33] modified this system for estimating the severity of splenic injury. The extent of splenic parenchymal injury was graded: one for a simple laceration, two for a fracture, and three for a shattered spleen. Additional points were given for hemoperitoneum confined to the left upper quadrant, hemoperitoneum remote from the spleen but not in the pelvis, and pelvic hemoperitoneum. The maximum score is six. These authors noted that nonoperative therapy was successful in all patients with scores between 1.0 and 2.5, whereas successful nonoperative treatment was possible in only 7 of 15 patients with scores between 2.5 and 5.5 points.[33]

The success of nonoperative splenic salvage after blunt trauma varies with progressive attitudinal changes among the surgeons providing emergency department coverage. These changes develop slowly, as demonstrated by the experiences of the William Beaumont Hospital in Royal Oak, Michigan. Some surgeons introduced nonoperative splenic salvage in 1978.[46] Opposition among colleagues was fierce and acceptance slow. Resistance lessened after 5 years, when nonoperative splenic salvage was achieved in 30% of injured patients and none of the observed patients required late splenectomy.[46] From 1984 through 1989, the success of nonoperative splenic salvage increased to almost 70% as 34 or 52 patients have been spared an unnecessary operation.[47] More importantly only 1 of the 18 patients requiring operation had isolated splenic injury and this patient never received any preoperative blood transfusions; his surgeon now admits operation was premature. All patients requiring blood transfusions (range, zero to seven units) during the course of nonoperative splenic salvage had associated injuries. Furthermore laparotomy in most of the 18 patients who were not candidates for nonoperative splenic salvage was dictated by the signs and symptoms of associated intra-abdominal injuries, including the liver, diaphragm, duodenum, pancreas, and intestine. The typical clinical course is presented in the following case summary.

### Case Report

A 30-year-old woman presented after a motor vehicle accident. She was a restrained driver struck on the left side. Positive findings included left lower thoracic and left upper abdominal pain and tenderness, and left knee and pubic tenderness. Roentgenograms and abdominal CT scan revealed a left seventh rib fracture, a class II splenic injury, and a pelvic fracture (Fig. 6). Treatment included intravenous crystalloids and bed rest. The initial hemoglobin of 11 g/dL decreased to a final value of 9.2 g/dL on day 2. Diet was initiated on day 3 and and patient resumed a regular diet by day 5. Discharge home was delayed until day 9 for orthopaedic considerations. Repeat abdominal CT scan at 5 weeks showed splenic healing (Fig. 7).

Another patient had successful nonoperative therapy of combined type II spleen and type II liver injuries, which foretells a future narrative on the nonoperative approach to blunt liver injury (Fig. 8). The 70% success rate of nonoperative splenic salvage achieved after blunt abdominal trauma in adults is surpassed by recent pediatric experience. Wesson reports that 85% of children with blunt splenic injury can be managed successfully without operation.[48] The guidelines for nonoperative splenic salvage are emerging. The stable patient without suspected intraperitoneal hollow viscus injury is a candidate for CT. Some degree of abdominal tenderness is common but this tenderness typically is much less than one sees with hollow

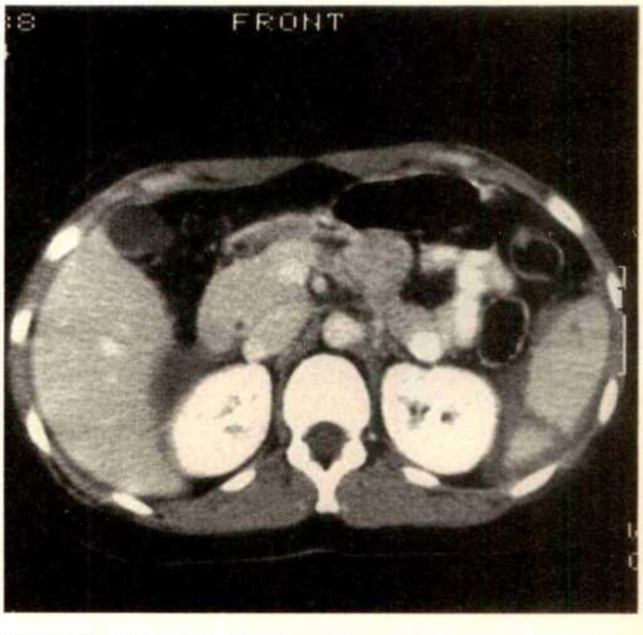

FIG. 6. Abdominal CT scan of this 30-year-old woman shows a type II splenic transection that was successfully treated nonoperatively (courtesy of Dr. Robert Lucas, Royal Oak, MI).

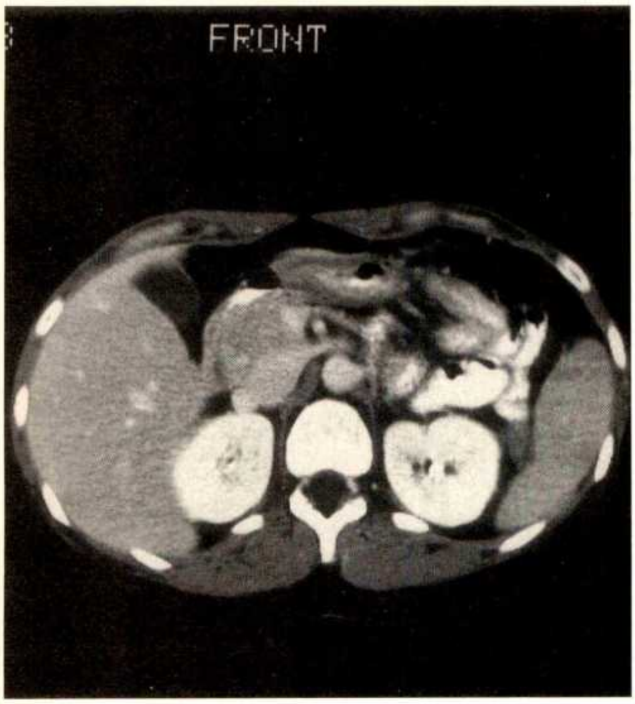

FIG. 7. Six weeks after splenic rupture, abdominal CT scan shows complete healing (Courtesy of Dr. Robert Lucas, Royal Oak, MI).

viscus perforation. When tenderness worsens during observation, exploration is indicated to preclude hollow viscus injury. Often the hemoglobin decreases and can be treated without transfusion when the hemoglobin remains more than 8 g/dL. Transfusion of two units of blood during the initial 48 hours to maintain the hemoglobin to more than 8 g/dL is compatible with successful nonoperative salvage. A further decrease in hemoglobin requires operative intervention unless the progressive anemia results from other injuries, especially fractures. The observing surgeon must be willing to reverse the choice of therapy whenever vital signs become unstable, more than two blood transfusions for splenic injury are needed, or when hollow viscus or retroperitoneal injury are suspected.

Critics of nonoperative splenic salvage in the adult patient emphasize the potential of overlooked hollow viscus perforation and the low incidence of operative splenic salvage in patients requiring late operative intervention.[49] Proponents for nonoperative splenic salvage suggest that hollow viscus perforation leads to early dramatic peritoneal signs in mentally alert patients and that nonoperative splenic salvage is contraindicated when one or more factors impairs mental competence. These proponents also rationalize that most patients who have successful splenorrhaphy could have been successfully observed nonoperatively. Probably there is a significant overlap so that the numbers of patients who can have successful splenorrhaphy but cannot be successfully observed is quite small. The threat of an overlooked diaphragmatic rupture should be small because most such injuries are apparent on plain films, whereas the remainder should be diagnosed by CT.[49]

### Splenic Wound Healing

Despite the phenomenal increase in splenic salvage by either operative splenorrhaphy or nonoperative observation,[18] few studies address the efficacy of splenic wound healing. Previous studies have suggested that patients treated by splenorrhaphy or by nonoperative observation need bed rest for 1 week and should avoid contact recreation for 6 months. Dulchavsky and coworkers[18] studied the efficacy of splenic wound healing in control canine and porcine models. They created multiple identical class II lacerations extending 5 cm in length and 1 cm in depth. Wound breaking strength (WBS) was monitored following splenorrhaphy and healing by second intent after temporary pack compression for hemostasis. These injuries did not extend into the splenic hilum. The WBS after splenorrhaphy equaled WBS of uninjured splenic tissue by 3 weeks in both these animal models. The WBS after healing by second intent equaled the WBS of uninjured splenic tissue by 6 weeks in both species (Fig. 9). The increase in WBS paralleled extensive capsular fibrosis and an exuberant fibrotic reaction at the splenorrhaphy site and along the intrasplenic septa. When no intrasplenic defects exist after either operative or nonoperative splenic salvage, return to normal activities, including contact sports, should be safe by 6 weeks.[18]

Not all splenic injuries show complete resolution on CT scan within 6 weeks after injury. Smith (personal communication) observed a 39-year-old motorcyclist after the diagnosis of class II splenic injury was made by CT scan (Fig. 10). During the first 48 hours, the patient received two transfusions for correction of anemia of 6.8 g/dL. When the hemoglobin slowly decreased to 7.3 g by

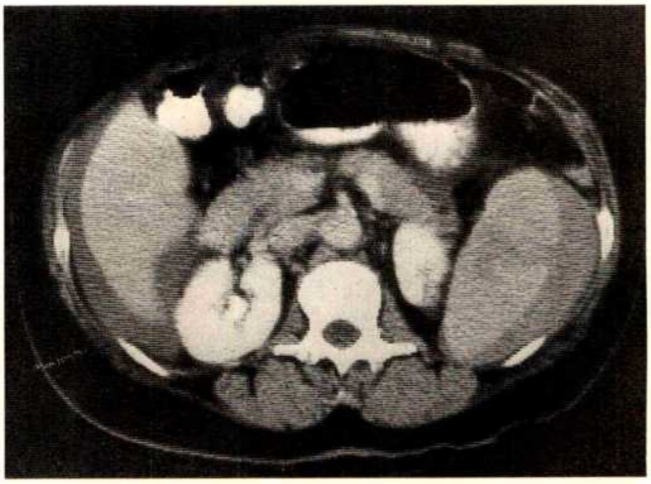

FIG. 8. Patient with type II splenic and type II liver injury (not shown) with parenchyma disruption and capsular tear, giving hemoperitoneum treated without operation. Total hospitalization was 4 days.

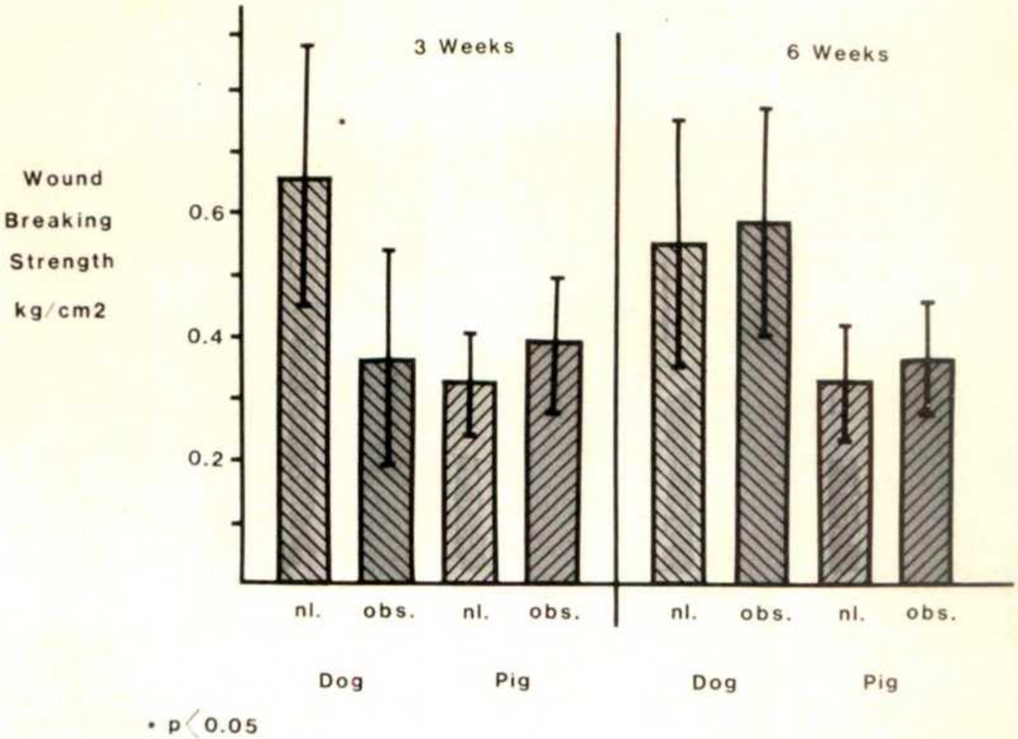

FIG. 9. Splenic wound-breaking strength recovers quickly after both splenorrhaphy and healing by second intent (obs) in canine and porcine models.

day 6, two additional blood transfusions were given. Shortly thereafter the adynamic ileus resolved and the patient was discharged on day 9. Follow-up abdominal CT scan 6 weeks later showed complete resolution of the hemoperitoneum but persistence of an intrasplenic hematoma (Fig. 11). No data on the potential for subsequent splenic rupture in this patient is available. Pending such data, the recommendation would be for continued avoidance of contact sports until a subsequent abdominal CT scan showed complete resolution of the intrasplenic hematoma.

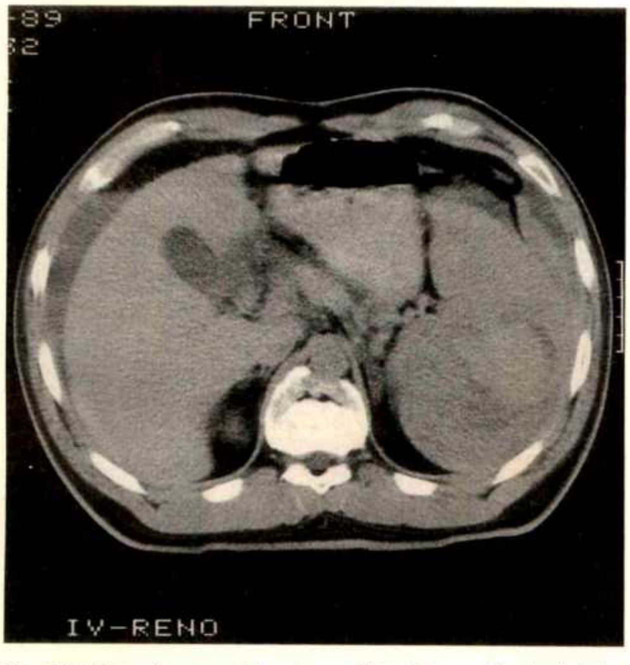

FIG. 10. Thirty-nine-year-old motor cyclist with type II splenic injury treated without operation (Courtesy of Dr. Randall Smith, Temple, TX).

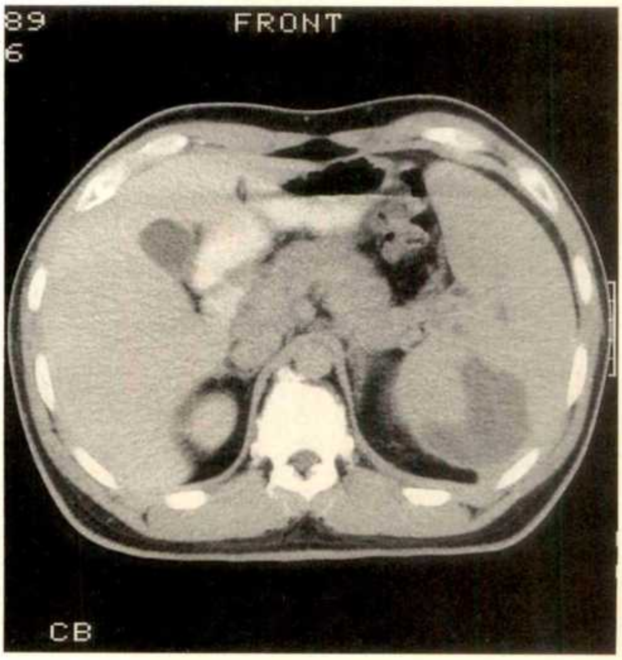

FIG. 11. Six weeks after nonoperative therapy for type II splenic injury (Fig. 10), residual intraparenchymal hematoma remains. Avoidance of contact sports is deferred until a repeat scan in 6 weeks. (Courtesy of Dr. Randall Smith, Temple, TX).

### Splenectomy

There always will be some patients who require splenectomy for preservation of life (Fig. 12). Consequently the guidelines for successful splenectomy and the approach to postoperative complications must be emphasized.[29] Successful splenectomy requires adherence to the above guidelines of full exposure after proper mobilization of the spleen and distal pancreas. After mobilization careful identification of the anatomic planes between the spleen and surrounding organs decreases inadvertent injury and postoperative complications. Postoperative hemorrhage, the most feared complication, is avoided by systematically identifying each splenic attachment and all the collateral vessels before division. Along the inferior pole of the spleen, there are two constant vessel groups that may be inadvertently torn while retracting the colon or stomach. The most inferior vessel group enters the spleen within 1 cm of the inferior border. The second vessel group penetrates the hilum approximately 1 cm superior to the previous vessels. The next series of vessels include the multiple branches from the splenic artery and vein that enter the mid portion of the splenic hilum. During splenectomy, these vessel groups should be identified carefully and clamped while taking care to avoid injury to the tail of the pancreas. If active bleeding impairs full visualization, the tip of the pancreas can be palpated, thereby permitting safe division of these vessel groups without pancreatic injury. Finally care must be taken to avoid injury to the short gastric vessels. Usually two vessel groups course from the superior splenic hilum to the most proximal portion of the greater curvature of the stomach. These vessels are torn easily when the cardioesophageal junction is pulled anteriorly or medially. With careful division of the proximal branches of the left gastroepiploic vessels, these short gastric vessels can be identified easily, doubly clamped, and divided. When ligating the gastric remnants of the short gastric vessels, care should be taken to avoid injury to the gastric wall. When postoperative hemorrhage occurs, the most likely source will be the short gastric vessels. During re-exploration, successful containment of hemorrhage is facilitated by rapid evacuation of the left upper quadrant clot, packing of the splenic bed, and inspection of the short gastric vessels. Less frequently bleeding will persist from the former splenic attachments to the posterior diaphragm, the retroperitoneal structures, or from one of the branches of the splenic vessels near the tail of the pancreas. Other complications of splenectomy include gastric fistula, pancreatic fistula, and colonic fistula due to clamping or tying these organs. This leads to necrosis and fistulization. Pancreatitis without fistulization may result from handling the pancreas too roughly during splenic mobilization. Usually this can be treated without operation.

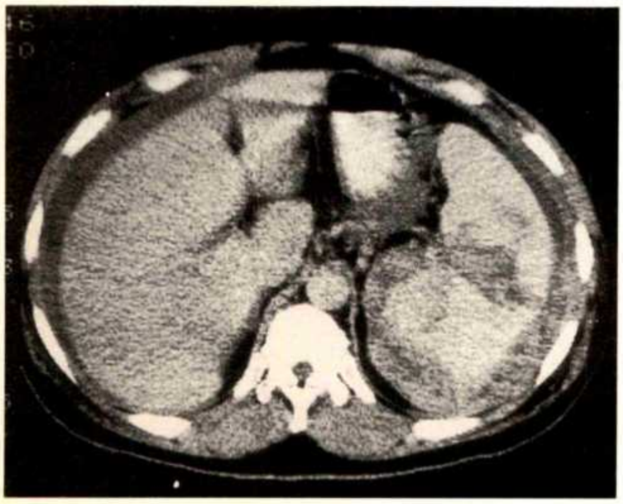

FIG. 12. After 72 hours of nonoperative therapy, this 32-year-old victim of blunt injury developed increased abdominal pain and new bleeding from this type III splenic injury extending through the hilar structures, necessitating laparotomy and splenectomy.

The role of drainage after splenectomy is also controversial. Whereas some type of drainage, usually with a Penrose drain, was once routine, most surgeons now use drainage selectively.[29-33] The author recommends drainage only for patients with associated colon injury, massive contamination from gastric or small bowel injury, or when some questions exist about the efficacy of hemostasis. In this instance, a soft rubber is brought out a 1-inch separate stab wound and enclosed within a colostomy bag to preclude stagnation of exuded fluid on saturated dressings surrounding the drain. Once drainage has ceased or decreased to less than 50 mL per 24 hours, the drain is removed. Usually this occurs by the second postoperative day before significant retrograde movement of bacteria from the skin to the subphrenic space occurs. Splenectomy also causes hematologic changes, especially with the platelets. A routine postsplenectomy thrombocytosis peaks at more than one million/mm$^3$ by the 10th day. This thrombocytosis is not an indication for anticoagulation because these platelets are old and do not promote clotting.

After successful splenectomy and postoperative management, the surgeon's responsibility for patient care does not end. The patient must be forewarned of the potential for OPSI and the need for prophylaxis against subsequent infection.[27,43,50] The polyvalent pneumococcal vaccines provide some degree of protection. When there is some question about patient compliance within postdischarge visits, this vaccine should be administered before discharge. Alternatively the vaccine can be administered during the follow-up office or clinic visits. The value of a booster injection with the polyvalent vaccine has not been determined yet. Powell and coworkers[27] demonstrated that the combination of polyvalent vaccine plus penicillin therapy would provide complete protection or survival after an intraperitoneal injection of *Streptococcus pneu-*

*moniae* in rodents. In contrast the polyvalent vaccine alone resulted in only a 25% survival rate compared to only a 5% survival rate in animals that were protected with neither the polyvalent vaccine nor the penicillin. The protection afforded by the combination of vaccine and penicillin was complete, regardless of whether the penicillin was given 3 days before or 1 day after the pneumococcal challenge. Zerrabi[50] supports the use of penicillin prophylaxis, emphasizing that the likelihood for OPSI in patients receiving prophylactic penicillin is very rare. This report must be put into perspective, however, because the incidence of OPSI in patients not receiving penicillin prophylaxis is also very uncommon.

Unfortunately the value of the polyvalent pneumococcal vaccine may be blunted by the multitude of organisms causing OPSI because many bacteria are not encapsulated or are not included in the spectrum covered by the polyvalent vaccine.[27] Furthermore some studies suggest that the efficacy of the polyvalent vaccine depends on the presence of splenic tissue.[26] Consequently the asplenic state would impair effective synthesis of antigens against the pneumococcal species. Amid these uncertainties, a reasonable course of action calls for the administration of the polyvalent vaccine before discharge in those patients thought to be noncompliant with office visits or following full recovery from the operative insult in patients seen in the office. In addition to the polyvalent vaccine, the patient should be informed of the potential for impaired immunologic defenses and be advised to communicate early with his treating physician for all infectious problems. Institution of early penicillin therapy or some similar antibiotic coverage for infectious problems should provide added protection against OPSI. Pending subsequent studies, the use of prophylactic antibiotic therapy in patients without infection is not recommended.

## References

1. Sherman R. Prospectives in management of trauma to the spleen: 1979 Presidential Address. American Association for the Surgery of Trauma. J Trauma 1980; 20:1-13.
2. Zaccarelli A. (Leonardo Fioravanti in Il Tesoro della Vita Humana (The Treasure of Human Life): Diviso in Libri Quattro, L. II, Cap. 8. Venetia, Appresso Gli Heredi di Melchior Sessa, 1570.
3. O'Brien E. Case of removal of the human spleen, without injury or derangement of the animal economy. Med Chir J Rev Lond 1816; 1:8-9.
4. Riegner O. Ueber einen Fall Von Exstirpation der Traumatisch Zerrissenen Milz. Berl Klin Wochnschr 1893; 30:177-181.
5. Aristotle. Parts of Animals, Book III Engl transl by A.L. Peck Cambridge, Mass. Harvard Univ. Press, 1955, Chapter 12.
6. Maimonides. Aphorisms of Moses. *In* Rosner F. The spleen in the talmud and other early Jewish writings. Bull Hist Med 1972; 46: 82-85.
7. Malpighi M. De Liene. *In* Malpighi M. De Viscerum Structura Exercitatio Anatomica. Bologna J Monitus 1666; pp. 101-150.
8. Pearce RM, Krumbhaar EB, Frazier CH. The history of extirpation of the spleen. *In* Pearce RM et al, eds.. The spleen and Anemia: Experimental and Clinical Studies. Philadelphia: JB Lippincott, 1918; pp 3-10.
9. Morris DH, Bullock FD. The importance of the spleen in resistance to infection. Ann Surg 1919; 70:513-521.
10. Bailey H. Traumatic rupture of the normal spleen. Br J Surg 1927; 15:40-46.
11. Moynihan BGA. Surgery of the spleen. *In* Keen WW, ed. Surgery; Principles and Practice, Vol. III. Philadelphia, WB Saunders 1908; pp. 1068-1093.
12. Pfeiffer DB, Smyth CM. Late result of splenectomy for traumatic rupture of the spleen. Ann Surg 1924; 80:562-568.
13. King H, Schumacker HB Jr. Splenic studies: I. Susceptibility to infection after splenectomy performed in infancy. Ann Surg 1952; 136:239-242.
14. Gofstein R, Gellis SS. Splenectomy in infancy and childhood. Am J Dis Child 1956; 91:566-569.
15. Hoefnagel R. Susceptibility of infection after splenectomy performed in childhood. Clin Proc Child Hosp 1956; 12:48-55.
16. Haller JA Jr, Jones EL. Effect of splenectomy on immunity and resistance to major infectious in early childhood: Clinical and experimental study. Ann Surg 1966; 163:902-908.
17. Smith CH, Erlandson M, Schulman I, Stern G. Hazard of severe infections in splenectomized infants and children. Am J Med 1957; 22:390-404.
18. Dulchavsky SA, Lucas CE, Ledgerwood AM, Grabow D. Wound healing of the injured spleen with and without splenorrhaphy. J Trauma 1987; 27:1155-1160.
19. Scher KS, Scott-Conner C, Jones CW, Wroczynski A. Methods of splenic preservation and their effect on clearance of pneumococcal bacteremia. Ann Surg 1985; 202:595-599.
20. Okinaga K, Giebink GS, Rich RH, et al. The effect of partial splenectomy on experimental pneumococcal bacteremia in an animal model. J Pediat Surg 1981; 16:717-724.
21. Llende M, Santiago-Delpin EA, Lavergne J. Immunological consequences of splenectomy: a review. J Surg Res 1986; 40:85-94.
22. Ohshio G, Manabe T, Tobe T, et al. The effect of splenectomy on antibody response to lipopolysaccharide (E. Coli) immunization. J Trauma 1988; 28:379-382.
23. Herbert JC. Pulmonary antipneumococcal defenses after hemisplenectomy. J Trauma 1989; 29:1217-1221.
24. Shennib H, Chiu RC, Mulder DS. The effects of splenectomy and splenic implantation on alveolar macrophage function. J Trauma 1983; 23:7-12.
25. Lau HT, Hardy MA, Altman RP. Decreased pulmonary alveolar macrophage bactericidal activity in splenectomized rats. J Surg Res 1983; 34:568-571.
26. Hosea SW, Burch CG, Brown EJ, et al. Impaired immune response of splenectomized patients to polyvalent pneumococcal vaccine. Lancet 1981; i:804-807.
27. Powell RW, Blaylock WE, Hoff CJ, Schartrand SA. The efficacy of post-splenectomy sepsis, prophylactic measures: the role of penicillin. J Trauma 1988; 28:1285-1288.
28. Dixon JA. Current laser applications in general surgery. Ann Surg 1988, 207:355-372.
29. Morgenstern L, Shapiro SJ. Techniques for splenic conservation. Arch Surg 1979; 114:449-454.
30. Buntain WL, Gould HR. Splenic trauma in children and techniques of splenic salvage. World J Surg 1985; 9:398-409.
31. Feliciano DV, Bitondo CG, Mattox KL, et al. A four year experience with splenectomy versus splenorrhaphy. Ann Surg 1985; 201: 568-575.
32. Moore FA, Moore EE, Moore GE, Millikan JS. Risk of splenic salvage following trauma: Analysis of 200 adults. Am J Surg 1984; 148: 800-805.
33. Rescinitti A, Fink MT, Raptopoulos V, et al. Nonoperative treatment of adult splenic trauma: development of a computed tomographic scoring system that detects appropriate candidates for expectant management. J Trauma 1988; 28:828-831.
34. Moorman DW, Evans DM, Wright DJ. Segmental splenectomy using the ultrasonic surgical aspirator. Am J Surg 1988; 155:266-267.
35. Schelling G, Block T, Gokel M, et al. Application of a fibrinogen-thrombin-collagen based hemostatic agent in experimental injury of liver and spleen. J Trauma 1988; 28:472-475.
36. Buntain WL, Lynn HB. Splenorrhaphy: changing concepts for the traumatized spleen. Surgery 1979; 86:748-760.

37. Delany HM, Porreca F, Mitsudo S, et al. Splenic capping: an experimental study of a new technique for splenorrhaphy using woven polyglycolic mesh. Ann Surg 1982; 196:187–193.
38. Rabo B, Ger R. Splenic preservation with the use of stapling instrument: A preliminary communication. J Trauma 1988; 28:117–119.
39. Leppaniemi A, Haapiainin R, Standertskjold-Nordenstam CG, et al. Delayed presentation of blunt splenic injury. Am J Surg 1988; 155:745–749.
40. Rhodes M, Lennard JWJ, Venables CW. Omental Abscess: a rare complication after implantation of autologous splenic tissue into the omentum. Br J Surg 1988; 75:288.
41. McIndoe AH. Delayed hemorrhage following traumatic rupture of the spleen. Br J Surg 1932; 20:249–268.
42. Sorkey AJ, Farnell MB, Williams HJ Jr, et al. The complementary roles of diagnostic peritoneal lavage and computed tomography in the evaluation of blunt abdominal trauma. Surgery 1989; 106: 794–801.
43. Buntain WL, Gould HR, Maull KI. Predictability of splenic salvage by computed tomography. J Trauma 1988; 28:24–34.
44. Reid B, Letts RM. Pediatric chance fracture: association with intra-abdominal injuries and seat belt use. J Trauma (In press).
45. Lutzker L, Koenigsber M, Meng CH, Freeman LM. The role of radionuclide imaging in splenic trauma. Radiology 1974; 110: 419–425.
46. Tom WW, Howells GA, Bree RL, et al. A nonoperative approach to the adult ruptured spleen sustained from blunt trauma. Am Surg 1985; 51:367–371.
47. Vallalba MR, Howells GA, Lucas RJ, et al. Nonoperative managemnet of the adult ruptured spleen Arch Surg 1990; 125:836–839.
48. Wesson DE. Traumatology today: old dogma, new directions—Presidential address 5th Annual Meeting Trauma Association of Canada. J Trauma 1989; 29:709–715.
49. Buckman RF Jr, Piano G, Dunham CM, et al. Major bowel and diaphragmatic injuries associated with blunt splenic or liver rupture. J Trauma 1988; 28:1317–1321.
50. Zarrabi MH, Rosner F. Rarity of failure of penicillin prophylaxis to prevent post-splenectomy sepsis. Arch Intern Med 1986; 146: 1207–1208.

# Rapid Analysis of Carcinoembryonic Antigen Levels in Gallbladder Bile

## *Identification of Patients at High Risk of Colorectal Liver Metastasis*

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**Recently it was found that immunoanalysis of carcinoembryonic antigen (CEA) levels in gallbladder bile may be a sensitive method to detect colorectal liver metastases in humans. Methods used in the past for the detection of CEA in various body fluids were cumbersome and time consuming, requiring acid extraction, extensive dialysis, and column purification. Single-step, solid-phase radioimmunoassays, designed specifically for serum CEA analysis, were developed commercially to replace these methods. Parameters and methodology necessary to adapt these kits for use with gallbladder bile are presented here. A combination of pretreatment procedures for bile, before radioimmunoassay, permit rapid, reproducible, and accurate measurement of CEA levels in gallbladder bile.**

CARCINOEMBYRIONIC ANTIGEN (CEA) is a 200,000 molecular weight (MW) glycoprotein that is excreted by certain embryonic and adult tissues in addition to adenocarcinomata of the digestive organs.[1] Extensive studies of patients bearing primary and metastatic colorectal neoplasms have determined that its primary use is in the detection of local and metastatic cancer recurrence after initial resection of the primary tumor, through periodic postoperative analysis of CEA in serum or plasma.[2]

Recently the notion that fluids bathing tumors in metastatic sites might contain higher levels of CEA than those found in the blood pool led us to analyze CEA levels in gallbladder bile from patients bearing colorectal liver metastases.[3] From these investigations, it was determined that CEA levels in gallbladder bile were strikingly higher than those in serum. Furthermore linear regression analysis of tumor volume *versus* gallbladder bile CEA levels in patients with liver metastases predicted that tumors as small as 1 $cm^3$ would produce easily measurable gallbladder bile CEA levels as high as 41 ng/mL. This data suggested that measuring biliary CEA levels in patients with primary colorectal lesions might permit detection of small, occult colorectal liver metastases earlier than is now possible through conventional methods (computed tomographic liver scanning, ultrasound, intraoperative exploration).

Previously used radioimmunoassays[4] were cumbersome and required lengthy dialysis; commercially available radioimmunoassays and enzyme-linked assays were designed only for serum CEA analysis. In addition we have found that the use of these assays required, at minimum, a 1:40 dilution of bile before analysis to dilute out an unknown interfering substance(s). This dilution process increased the lowest level of detectable CEA from 1 ± 0.9 ng/mL to 40 ± 0.9 ng/mL and limited the predictive, clinical use of the assay.

We designed a new, clinically applicable method for analysis of CEA levels in bile samples, which may be completed in approximately 6 hours. Using perchloric acid to extract CEA from other interfering biliary components (*i.e.*, bilirubin, proteins), followed by neutralization, dilution, and ultrafiltration, we were able to assay rapidly and accurately for CEA levels ranging from 5 to more than 40 ng/mL with a solid-phase, two-site radioimmunoassay.

## Materials and Methods

### *Specimens*

Gallbladder bile for analysis was obtained from patients without biliary pathology (controls) and from patients bearing colorectal liver metastases. All samples were ob-

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‡ Deceased.

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tained in accordance with the policies of the Institutional Review Board of the University of Florida, Gainesville, Florida.

*Reagents and Equipment*

Carcinoembryonic antigen solid-phase, two-site radioimmunoassay test kits were provided by Hybritech, Inc. (San Diego, CA). These kits contained human serum standardized samples with known levels of CEA from 0 to 100 ng/mL to be used as standards in analysis. Also included in the kit were murine monoclonal anti-CEA antibody-coated plastic beads and $^{125}$I-labeled murine monoclonal IgG tracer anti-CEA antibodies (directed against an antigenic site distinct from that detected by the solid-phase antibody). Centricon 30,000 MW cutoff ultrafiltration microconcentrators were purchased from Amicon, Inc. (Danvers, MA). Dialysis was performed using a 28-well microdialyzing system (Bethesda Research Laboratories, Gaithersburg, MD). Gamma counting was performed using an automated gamma counter (LKB/Wallac, Turku, Finland). A microfuge (Beckman-B, Beckman Instruments, Palo Alto, CA) was used to remove precipitates from perchloric acid extracts and a fixed-angle rotor (Beckman JA-20) was used for ultrafiltration.

*CEA Analysis by Solid-phase Radioimmunoassay*

The methodology used in the 4-hour radioimmunoassay test by Hybritech for CEA analysis previously was described in detail and has a sensitivity of 1.0 ± 0.9 ng/ml.[5] Briefly, following single-step incubation (at 37 C) of samples (100 $\mu$L), $^{125}$I-labeled tracer antibody (100 $\mu$L), and antibody-coated beads, a standard curve was constructed from linear regression analysis of values from CEA serum standards and used to determine experimental values.

*Specimens for Assay Standardization*

Serum standard reagents (provided in the Hybritech kit) were used to add known amounts of exogenous CEA to gallbladder bile obtained from normal patients (without endogenous CEA) and from patients bearing colorectal liver metastases (with endogenous CEA). For each admixed sample (to which exogenous CEA was added), in addition to known serum standard samples used as controls, an expected CEA level was compared with levels measured by radioimmunoassay before or after sample preparation.

*Sample Preparation Before CEA Analysis*

*Method 1 (2 hours).* Serum and admixed gallbladder bile standard samples (100 $\mu$L) were analyzed after a 2-hour pretreatment procedure. This procedure involved extraction with 0.5 mL of 1.2 mol/L (molar) perchloric acid for 30 minutes at room temperature and centrifugation at 9000*g* for 10 minutes to remove any precipitate. Supernatants were collected and neutralized with 0.5 mL of 1.0 mol/L TRIS in 0.15 mol/L phosphate-buffered NaCl (PBS), pH = 10.5. Samples then were brought up to 2.5 mL final volume with 0.15 mol/L PBS. These samples were concentrated by ultrafiltration using 30,000 MW cutoff microconcentrators (Amicon) for 30 minutes to 1 hour at 5000*g* (using a fixed-angle rotor at 32°). Retentate (40 ± 5 $\mu$L) once again was resuspended to 2 mL with 0.15 mol/L PBS and concentrated through ultrafiltration for 30 to 60 minutes. Centrifugation times varied with the amount of biliary pigment soluble in perchloric acid; longer periods of centrifugation were required for samples with larger concentrations of soluble pigment. Final retentate (40 ± 5 $\mu$L) was measured and mixed with approximately 60 $\mu$L CEA-free serum standard to yield 100 $\mu$L total sample volume for CEA radioimmunoassay.

*Method 2 (72 hours).* Serum and composite gallbladder bile standard samples (100 $\mu$L) were analyzed after extraction with 100 $\mu$L of 1.2 mol/L perchloric acid (30 minutes at room temperature), centrifugation to remove any precipitate at 9000*g* for 10 minutes, and supernatant collection. The supernatants were dialyzed (10,000 MW cutoff dialysis membranes) against four changes of distilled water (16 L total) for 72 hours and CEA levels were measured directly by radioimmunoassay.

## Results

Standard serum samples (containing 100 ng/mL CEA), when diluted with CEA-free serum, produced a linear dilution curve with the 'expected' CEA recovered at each dilution. When CEA was admixed with normal bile (undetectable endogenous CEA content), however, radioimmunoassay did not accurately yield the expected amount of CEA until the admixed bile sample was diluted approximately 40 times (Fig. 1). This limitation severely reduced the sensitivity of CEA determinations in bile such that levels less than 40 ng/mL could not be detected accurately by this method (*i.e.*, a 1:40 dilution of bile containing less than 40 ng/mL would reduce the measurable CEA content to an undetectable level of less than 1 ng/mL).

To remove the substance(s) interfering with the direct assay of bile, we used perchloric acid to maintain CEA solubility while precipitating out proteins and pigments (method 1). After this extraction, samples were neutralized with TRIS, concentrated and dialyzed simultaneously by ultrafiltration, and tested in solid-phase radioimmunoassay (6 hours total time for method). Expected levels of CEA in the serum and bile samples were compared with measured CEA levels (Fig. 2). Levels of exogenously added

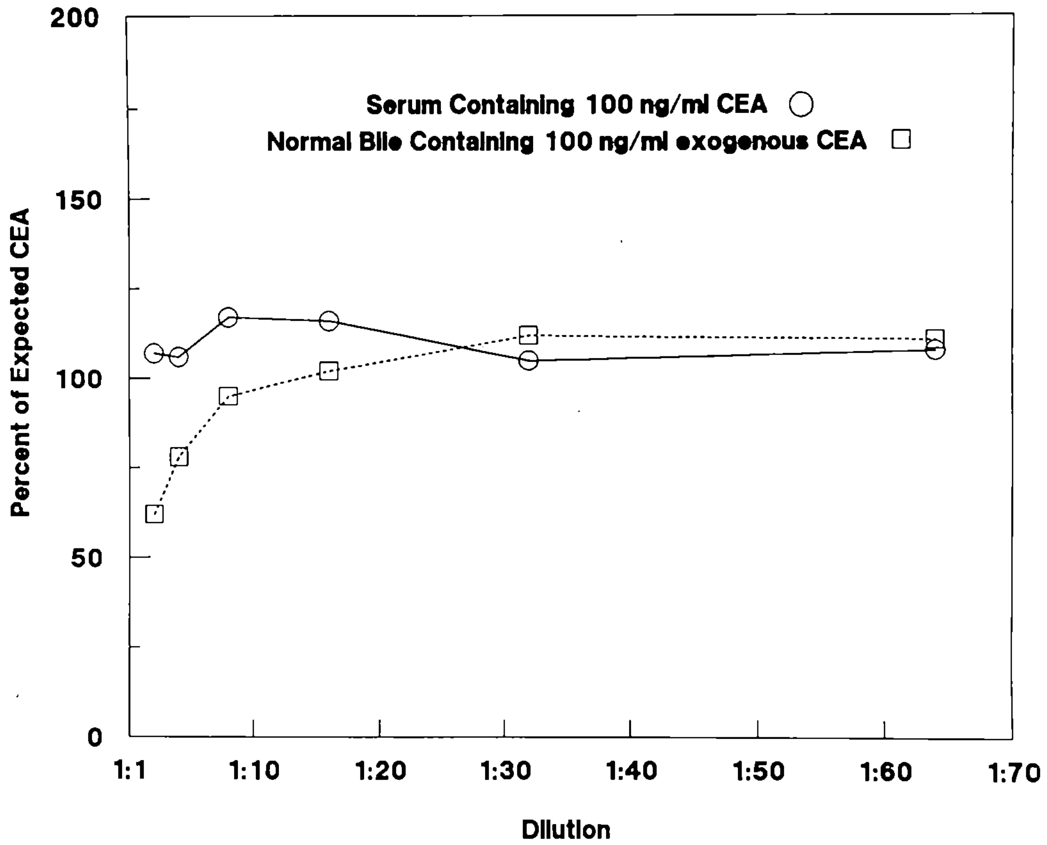

FIG. 1. Both standard serum samples (containing 100 ng/mL endogenous CEA) and normal bile samples (undetectable CEA) admixed 1:1 with standard serum samples (containing 200 ng/mL CEA) were analyzed directly by radioimmunoassay after dilution with CEA-free serum. Percentage of expected CEA was determined by comparing predicted with measured CEA levels at various dilutions. Accurate measurement of CEA levels in gallbladder bile, unlike serum, required 40-fold dilution (dilution factor includes the 1:1 dilution incurred during admixing) to remove inhibitory substance(s).

CEA as low as 5 ng/mL were measured accurately and reproducibly from serum, normal bile, and 'metastatic bile' (known to contain 32.4 ng/mL endogenous CEA). Expected levels of CEA for metastatic bile were determined by adding the known value of endogenous CEA, measured by 1:40 dilution of bile, to the amount of exogenous CEA admixed with the bile before analysis. Pearson correlation coefficients were all very high (0.997) and were associated with low root mean square (RMS) errors (≤ 2.3).

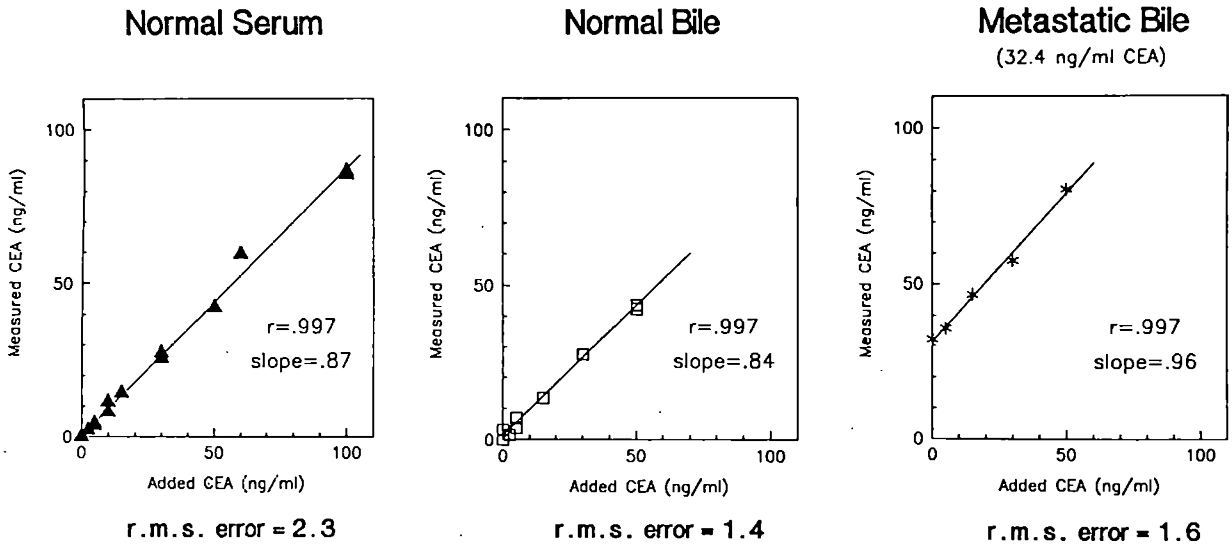

FIG. 2. Specimens were pretreated by perchloric acid extraction without dialysis (method 1) before analysis. Measurement of CEA concentrations in normal serum (endogenous CEA, 0 ng/mL), normal bile (endogenous CEA, 0 ng/mL), and 'metastatic' bile obtained from a patient with documented colorectal liver metastasis (endogenous CEA, 32.4 ng/mL) after the addition of various amounts of exogenous CEA demonstrates that expected CEA levels (based on the known amounts of CEA added to each sample) correlate closely with measured CEA levels using this method.

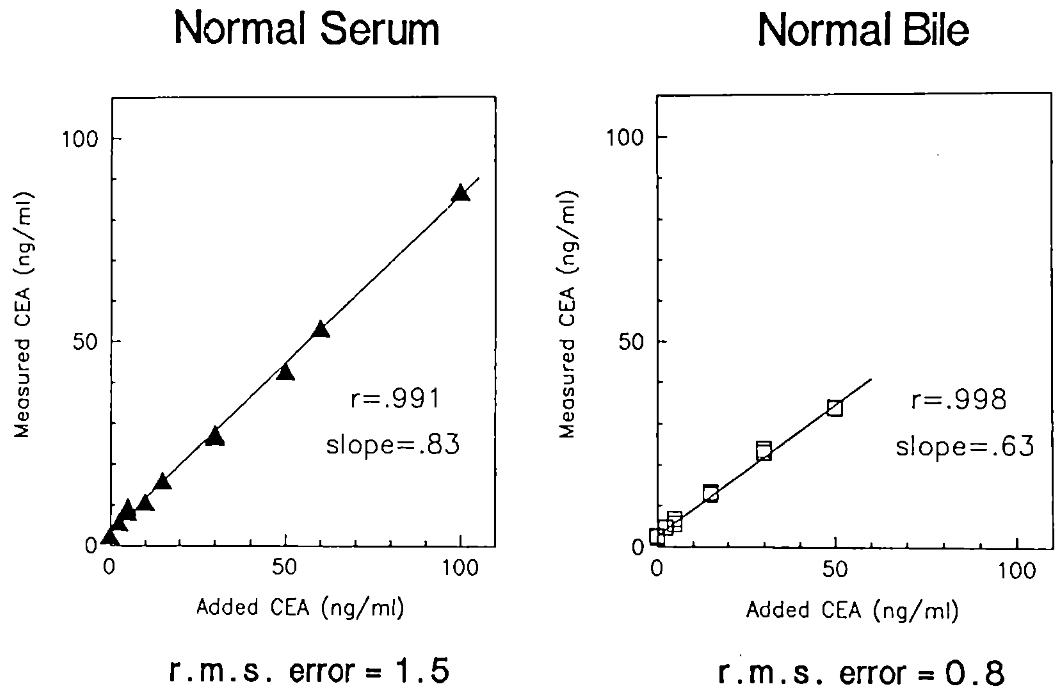

FIG. 3. Specimens were pretreated by perchloric acid extraction with 72 hours of dialysis (method 2) before analysis. Measurement of CEA concentrations in normal serum (endogenous CEA, 0 ng/mL) and normal bile after the addition of various amounts of exogenous CEA demonstrates high correlation between expected CEA levels and measured CEA levels using this method.

The results of the 6-hour assay using ultrafiltration for concentration and dialysis (method 1) were paired to those obtained from the 72-hour assay (method 2), which required extensive dialysis and often generated errors in estimation of subsequent sample volume (Fig. 3). From this data it is clear that similar results are obtained for most samples using either method 1 or 2; however, for samples containing higher levels of CEA (30 and 50 ng/mL) added to bile, dialysis does not appear to remove completely all the inhibitory factors because CEA levels significantly lower than expected were recovered.

While the sensitivity and reproducibility of the Hybritech assay is known for serum CEA analysis, these values have not been established yet for gallbladder bile. To determine the precision of this CEA radioimmunoassay for use with bile specimens, we first examined the variation of the assay for determining CEA levels in the same replicate groups (Table 1). Four normal (undetectable CEA content) bile samples were admixed with known amounts of CEA provided in the Hybritech kit, pretreated by method 1, and aliquoted into multiple groups or replicates (3 to 5 aliquots per sample). These aliquots then were assayed for CEA content. The data in Table 1 demonstrate that, for each of the four CEA levels (12.3 to 60.0 ng/mL), the variability of measured CEA levels within replicates is quite low, with standard deviations ranging from 0.4 to 3.9 and coefficients of variation ranging from 3.4% to 7.5%.

Having established the reproducibility of the assay for the detection of CEA within the same pretreated/aliquoted specimen, we examined the variability of results obtained first by individually processing (pretreating) multiple aliquots of the same bile sample (endogenous CEA level known to be 12.5 ng/mL) and then measuring CEA content (Table 2). In other words, we measured the variation inherent in the pretreatment procedures for the bile. Once again variability among replicates was low (standard deviations ranged from 0.5 to 1.8) and the mean CEA levels detected within each separate, pretreated aliquot (samples 1 to 3) were almost identical (11.6 to 12.9 ng/mL).

## Discussion

The sensitivity of gallbladder bile CEA analysis for detecting colorectal liver metastases has been shown to be

TABLE 1. *Precision of Bile Assay (Method 1): Within Assay Variation*

| Sample | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Number of replicates | 3 | 5 | 5 | 5 |
| Mean CEA level (ng/mL) | 12.3 | 16.7 | 33.1 | 60.0 |
| Standard deviation | 0.4 | 1.3 | 1.3 | 3.9 |
| Coefficient of variation | 3.4% | 7.5% | 3.9% | 6.4% |

CEA, carcinoembryonic antigen.

TABLE 2. *Precision of Bile Assay (Method 1): Within Sample Variation*

| Sample | 1 | 2 | 3 |
|---|---|---|---|
| Number of replicates | 3 | 3 | 3 |
| Mean CEA level (ng/mL) | 11.6 | 12.3 | 12.9 |
| Standard deviation | 0.5 | 0.4 | 1.8 |
| Coefficient of variation | 4.6% | 3.4% | 13.8% |

CEA, carcinoembryonic antigen.

TABLE 3. *Analysis of Serum and Gallbladder Bile CEA Levels in Control Patients and in Patients with Known Colorectal Liver Metastases*

| | | CEA Levels (ng/mL)* | |
|---|---|---|---|
| Group | n | Serum | Bile |
| Normal controls | 5 | 0.8 ± 0.5 | 0.2 ± 0.1 |
| Liver metastases | 16 | 58.1 ± 23.8† | 1574.0 ± 380.2† |

* Values represent mean carcinoembryonic antigen (CEA) levels ± standard error of the mean.

† p = 0.0009.

superior to serum CEA analysis.[3] Control patients with normal livers had low serum and bile CEA levels, whereas patients with colorectal liver metastases had CEA levels in bile markedly greater (up to 259 times greater) than serum (Table 3). With knowledge of the potential for biliary CEA analysis to detect colorectal liver metastases and to identify patients with occult hepatic metastases, a rapid, reliable assay was needed for clinical application.

Initial attempts to measure CEA levels in gallbladder bile demonstrated that an inhibitor(s) was present in all bile samples (n = 45) tested.[3] For this reason available assay test kits (designed for serum) are not suitable for the detection of CEA levels less than 40 ng/mL in bile because a 1:40 dilution is required before analysis to remove the inhibitor(s).

We developed a new quantitative assay for detecting CEA in bile that represents a significant improvement over previous methodologies designed for serum. Perchloric acid extraction of bile, along with neutralization and ultrafiltration, were used to separate CEA from interfering biliary substances. Solid-phase radioimmunoassay then was used to measure directly CEA levels.

With this new methodology, CEA analysis of gallbladder bile is now possible, without end-sample dilution or loss, in approximately 6 hours. At levels of detection as low as 5.0 ± 0.9 ng/mL, we hope to detect occult colorectal liver lesions producing low levels of CEA in the bile (0 to 40 ng/mL) that now escape routine methods of detection. Prospective clinical trials are underway using this new method for CEA analysis of bile to evaluate fully its potential for early detection of colorectal liver metastases.

## Acknowledgments

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## References

1. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965; 121:439–462.
2. Steele G, Ellenberg S, Ramming K, et al. CEA monitoring among patients in multi-institutional adjuvant G.I. therapy protocols. Ann Surg 1982; 196(2):162.
3. Yeatman TJ, Bland KI, Hollenbeck JI, et al. Relationship between colorectal liver metastases and CEA levels in gallbladder bile. Ann Surg 1989; 210(4):505–512.
4. Hansen HJ, Snyder JJ, Miller E, et al. Carcinoembryonic antigen (CEA) assay. Human Path 1974; 5(2):139.
5. Hybritech, Inc. Monograph. Tandem-R CEA Immunoradiometric Assay: for the quantitative measurement of carcinoembryonic antigen (CEA) in serum; 1985, pp 1–7.

# Liver Transplantation for Hepatoblastoma

## *The American Experience*

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**The current role of liver transplantation in treating malignant tumors of the liver is uncertain, except for select histologic types. Pooled data on the results of liver transplantation in 12 children with hepatoblastoma is presented here. One half of the children are alive 24 to 70 (44 ± 19) months after transplantation with no evidence of recurrence. Three patients (25%) died of tumor recurrence and three (25%) died of other causes. Unifocal and intrahepatic tumors were associated with better prognosis compared to the multifocal tumors and tumors with extrahepatic spread ($p = 0.04$ and 0.13). Microscopically vascular invasion and the predominance of embryonal and/or anaplastic epithelium were associated with a poor prognosis compared to the tumors with no vascular invasion and with predominantly fetal epithelium ($p = 0.08$ and 0.1). It is concluded that continued efforts to treat unresectable hepatoblastomas by liver transplantation is justified and the role of adjuvant chemotherapy in improving the results needs to be better defined.**

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AT THE TIME of the initial trials of clinical liver transplantation, the ideal indication was perceived to be a malignant tumor confined to the liver that could not be removed with partial hepatic resection.[1,2] However efforts to apply this concept were disillusioning because the incidence of recurrence after orthotopic liver transplantation was very high.[3] Nevertheless some malignant tumors in adults have been treated effectively with total hepatectomy and replacement of the liver.[4–7]

The possibility that hepatoblastoma should be considered in a special category was suggested by anecdotal accounts of children surviving for long periods after liver replacement for this indication. However there are no reports of a significant number of cases as to the long-term results of liver transplantation for hepatoblastoma.[7] We report here observations in 12 children with hepatoblastomas who were treated by liver transplantation in the United States.

## Case Material

As of August 1988, 12 children had received 13 liver grafts for hepatoblastoma in 10 different medical centers in the United States. Data were collected on all patients regarding age, sex, previous liver resection, chemotherapy before and after the transplant, extent of gross disease at the time of transplant, recurrence after the transplant, and the patients' current clinical status (Table 1). Information on the histologic features of the tumors was obtained through review of the surgical pathology reports and, when necessary, by direct contact with the examining pathologists.

The 12 children were aged from 6 months to 11 years (42 ± 33 months); 6 were girls. Four underwent a hepatic resection 9 to 20 months before their transplant in an attempt to control the tumor. All children had markedly elevated serum alpha-feto-protein levels at the time of their transplantation. Only 1 of the 12 children had cirrhosis.

### *Extent of Gross Disease at Transplantation*

The disease was entirely intrahepatic in six patients. Although another three patients had intrahepatic tumor, a tumor thrombus was also present in the main portal vein. The remaining three patients were thought to have direct extrahepatic tumor invasion at the time of surgery. However, in one of these patients, the excised portion of the right hemidiaphragm was merely adherent to the tumor with no histologic invasion. In seven patients with multifocal tumors the largest of the nodules measured 2.5 to 9.0 (m = 5.4) cm. Five patients had unifocal tumors infiltrating both lobes and/or the hilum of the liver. The size of these tumors varied form 5 to 18 (m = 12) cm in diameter.

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TABLE 1. *Patients with Hepatoblastoma Treated by Liver Transplantation*

| Age, Sex | Prior Hepatic Resection | Pre-TX Chemo. | Gross Disease | Histologic Features | Post-TX Chemo. | Recurrence | Status |
|---|---|---|---|---|---|---|---|
| 1.75 yrs.<br>M | Yes | Yes | IH<br>Unifocal | Predominantly F<br>No vascular invasion | No | No | Died of Pneumocystis Pneumonitis; 9 mos. |
| 4.5 yrs.<br>M | Yes | Yes | IH + TT<br>Multifocal | F + E<br>Vascular invasion+ | Yes | Yes<br>Peritoneum; brain | Died of recurrence; 23 mos. |
| 5 yrs.<br>F | Yes | Yes | IH + TT<br>Multifocal | Predominantly E<br>Vascular invasion+ | No | No | Died of hepatic artery thrombosis; 15 days |
| 0.5 yrs.<br>M | No | No | IH; Unifocal | E + A; No vascular invasion | No | No | Died of hepatic artery thrombosis; 4 mos. |
| 1.5 yrs.<br>F | No | No | IH; Unifocal | F; No vascular invasion | No | No | Alive; 66 mos. |
| 4 yrs.<br>M | Yes | Yes | IH<br>Multifocal | E; Vascular invasion+ | No | Yes<br>Lungs; liver | Died of recurrence; 4 mos. |
| 11 yrs.<br>F | No | Yes | IH; Unifocal | F + E; No vascular invasion | Yes | No | Alive; 30 mos. |
| 5 yrs.<br>M | No | Yes | IH<br>Multifocal | A; Vascular invasion+ | No | No | Alive; 43 mos. |
| 3 yrs.<br>F | No | Yes | IH + TT<br>Unifocal | Predominantly F<br>Vascular invasion+ | Yes | No | Alive; 32 mos. |
| 2.5 yrs.<br>F | No | No | EH<br>Multifocal | F + E; Vascular invasion+ | Yes | No | Alive; 24 mos. |
| 2 yrs.<br>F | No | Yes | EH + Multifocal | F + E + A<br>Vascular invasion+<br>Lymph node+ | No | Yes<br>Brain; lungs | Died of recurrence; 35 days |
| 2.3 yrs.<br>M | No | Yes | IH<br>Multifocal | E + A; Vascular invasion+ | Yes | Yes<br>Pulmonary<br>7 mos. | Alive; 70 mos. |

IH, intrahepatic; EH, extra hepatic extension; TT, tumor thrombus in the main portal vein; F, fetal epithelium; E, embryonal epithelium; A, anaplastic epithelium.

### *Histologic Characteristics*

In nine (75%) patients, the tumors contained only epithelial elements. In three (25%), a variable amount of mesenchymal components also were present. Three patients had a purely or predominantly fetal epithelium. Embryonal and anaplastic epithelial patterns predominated in two patients each. There was an admixture of two or three epithelial patterns with no pattern predominating in five (42%) patients. Anaplastic epithelium was a component in three of these latter five patients.

Vascular invasion was evident microscopically in eight patients, including all three with tumor thrombii in the main portal vein. Only one child in the group of 12 had lymph node metastases and positive hepatic resection margins. Her tumor extensively infiltrated the rectus sheath, diaphragm and the pericardium.

### *Chemotherapy*

Nine patients received chemotherapy before and five after the transplant under different protocols (Table 1).

### *Statistical Analysis*

The median patient survival rate was calculated among the various groups and a nonparametric test (log rank test) was used to assess the statistical significance of the differences in the length of survival. A p value of 0.05 or less was considered significant.

## Results

### *Survival*

Six of the twelve children with hepatoblastoma died after transplant. Three died due to recurrent disease at 35 days, 4 and 23 months after transplantation. All three had multiple sites of recurrence. Two children died of allograft hepatic artery thrombosis, one despite retransplantation, 15 days and 4 months after operation, respectively. The sixth child died of Pneumocystis pneumonitis 9 months after transplantation. Autopsies performed in the latter two patients did not reveal any evidence of tumor.

The remaining six children are alive 24 to 70 (44 ± 19) months after transplantation with no evidence of malignancy. The longest surviving child developed a solitary pulmonary metastasis 7 months after his transplant despite adjuvant post-transplant chemotherapy. This was resected and he remains tumor free with 70 months of follow-up. All survivors have had good allograft function. One patient developed a lymphoproliferative disorder 2 years after transplantation that resolved with the reduction of cyclosporine.

The deaths due to recurrent disease and the duration of survival have been analyzed further in relation to the factors listed below.

(1) Previous liver resection: two of the four patients (50%) who underwent hepatic resection before the transplant died of recurrent tumor compared to one of the eight patients (13%) without a previous resection.

(2) Extent of gross disease (Table 2): in children with unifocal tumors, no deaths occurred due to recurrent disease and they survived significantly longer than did those children with multifocal tumors (p = 0.04). Similarly intrahepatic tumors had a better prognosis than did tumors manifesting portal vein tumor thrombus or direct extrahepatic invasion. The difference in their median survival times, however, did not reach statistical significance (p = 0.13). The child with lymph node involvement died of cerebral metastases 35 days after the transplantation.

(3) Histology (Table 2): microscopic evidence of vascular invasion and the presence of embryonal and/or anaplastic epithelium in the tumors were associated with poor prognosis. These differences, however, did not reach statistical significance (p = 0.08 and 0.1, respectively).

(4) Chemotherapy: three of the nine children who received chemotherapy before transplantation died of recurrence. One of the five (20%) children who received post-transplant chemotherapy and two of the seven (28%) who did not receive chemotherapy died as a result of recurrent tumor.

## Discussion

Hepatoblastoma is the most common primary malignant liver tumor in children younger than 5 years.[8,9] Partial hepatic resection is the standard form of curative therapy. In recent years preoperative chemotherapy has allowed resection of previously unresectable tumors.[10-12]

TABLE 2. *Extent of Gross Disease and Histologic Features Correlated to the Outcome*

| Prognostic Tumor Characteristics | Deaths Due to Recurrent Disease | Median Survival in Months | |
|---|---|---|---|
| Extent of Disease at Surgery | | | |
| Unifocal | 0/5 | 30 | p = 0.04 |
| Multifocal | 3/7 (43%) | 5 | |
| Intrahepatic | 1/7 (14%) | 30 | p = 0.13 |
| Extrahepatic | 2/5 (40%) | 5 | |
| Histologic Characteristic | | | |
| Vascular invasion | | | |
| Present | 3/8 (38%) | 14.5 | p = 0.08 |
| Absent | 0/4 | 19.5 | |
| Type of epithelium | | | |
| Fetal | 0/3 | 32 | p = 0.10 |
| Nonfetal or mixed | 3/9 | 5 | |

Total hepatectomy and orthotopic liver transplantation becomes a rational choice for tumors that are unresectable by conventional means. Application of this concept to treat unresectable hepatocellular carcinoma has had a high incidence of recurrence and death after transplantation.[2-7] Long-term survival after transplantation for hepatoblastoma previously has been reported only for one patient surviving 6 years after transplantation.[7]

The results of liver transplantation for hepatoblastoma in this series is inferior compared to the overall survival rate of pediatric liver recipients (58% *versus* 71% 2-year survival rate).[13] However this compares favorably to the 20% to 30% 2-year survival rates reported after transplantation for hepatocellular carcinoma.[3,7]

Children who had a hepatic resection before transplantation appeared to have worse prognoses compared to the children who did not. The reason is unknown but might be due to the more aggressive nature of the recurrent tumors. Various clinicopathologic correlations have been made to identify prognostic factors that affect survival in children with hepatoblastoma. The size of the tumor alone has not been shown to be significant as long as it is resectable.[9,14] In this series the unifocal tumors were generally much larger than the multifocal tumors (d = 12 cm *versus* 5.4 cm) but had a significantly better prognosis. Extent of gross disease evident at surgery appears to have a definite impact on survival after transplantation. Patients with only intrahepatic tumors had better survival rates compared to the patients with extrahepatic extension.

Kasai and Watanabe[15] and subsequently other authors[8,14,16-18] reported the favorable prognosis associated with fetal epithelium in the tumors compared to that for the embryonal and anaplastic types. In this series also, patients with pure or predominantly fetal epithelial tumors did better. Vascular invasion had a negative impact on survival. The percentage of tumors containing mesenchymal elements varies among various reports and their prognostic significance is uncertain.[15,18,19] In this study the presence of mesenchymal elements in the tumors did not appear to affect the prognosis.

Reduced rates of recurrence have been reported with combination chemotherapy following a curative resection for hepatablastoma.[12] However our observations regarding the role of chemotherapy are inconclusive because of the small number of patients in each group and also because of the different protocols used.

In conclusion liver transplantation should be considered for nonmetastatic unresectable hepatoblastoma. The future role of pre- and post-transplant chemotherapy in improving the results remains to be defined.

## Acknowledgments

The authors thank James Williams, M.D. (Chicago) and Walter Andrews, M.D. (Dallas) for allowing us to include their patients in this series. The authors also appreciate the follow-up information provided by Edwin Douglas, M.D. (Memphis) on some of the patients.

## References

1. Starzl TE (with the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969; pp 350–373.
2. Calne RY, Williams R. Liver transplantation in man. I. Observations on the technique and organization in 5 cases. Br Med J 1968; 4: 535–540.
3. Iwatsuki S, Gordon RD, Shaw BW, et al. Role of liver transplantation in cancer therapy. Ann Surg 1985; 202:401–407.
4. Pichlmayr R. Is there a place for liver grafting for malignancy? Transplant Proc 1988; 20(Suppl 1):478–482.
5. Koneru B, Cassavilla A, Bowman J, et al. Liver transplantation for malignant tumors. Gastroenterol Clin North Am 1988; 17:177–193.
6. O'Grady JG, Polson RJ, Rolles K, et al. Liver transplantation for malignant disease. Ann Surg 1988; 207:373–379.
7. Ringe B, Wittekind C, Bechstein WO, et al. The role of liver transplantation in hepatobiliary malignancy. Ann Surg 1989; 209:88–98.
8. Lack EE, Neave C, Vawter GF. Hepatoblastoma: a clinical and pathological study of 54 cases. Am J Surg Pathol 1982; 6:693–705.
9. Exelby PR, Filler RM, Grosfeld JL. Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma. J Ped Surg 1975; 10:329–338.
10. Mahour GH, Udo Wogu G, Siegel SE, et al. Improved survival in infants and children with primary malignant liver tumors. Am J Surg 1983; 146:236–240.
11. Price JB, Schillinger JN, Santulli TV. Major hepatic resections for neoplasia in children. Arch Surg 1982; 117:1139–1141.
12. Evans AE, Land VJ, Newton WA, et al. Combination chemotherapy in the treatment of children with malignant hepatoma. Cancer 1982; 50:821–826.
13. Iwatsuki S, Starzl TE, Todo S, et al. Experience in 1,000 liver transplants under cyclosporine-steroid therapy: a survival report. Transplant Proc 1988; 20(Suppl 1):498–504.
14. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Human Pathol 1983; 14:512–537.
15. Kasai M, Watanabe I. Histologic classification of liver cell carcinoma in infancy and childhood and its clinical evaluation. A study of 70 cases collected in Japan. Cancer 1970; 25:551–563.
16. Watanabe I. Histopathological features of liver cell carcinoma in infancy and childhood and their relations to surgical prognosis. Jpn J Ca Clinics 1977; 23:691.
17. Foster JH, Berman MM. Solid liver tumors. Philadelphia: WB Saunders, 1977, pp 126–127.
18. Gonzalez-Crussi F, Upton MP, Maurer HS. Hepatoblastoma: attempt at characterization of histologic subtypes. Am J Surg Pathol 1982; 6:599–612.
19. Ishak KG, Glunz PR. Hepatoblastoma and hepatocellular carcinoma in infancy and childhood. Cancer 1967; 20:396–422.

# Adenocarcinoma in Barrett's Esophagus

## *A Clinicopathologic Study of 65 Cases*

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The natural history of Barrett's esophagus, particularly the prevalence and incidence of malignant changes in it, remains controversial. Furthermore the prognosis of surgically treated patients with carcinoma in Barrett's esophagus has not been elucidated fully. To examine these and other issues, the records of 65 patients with carcinoma in Barrett's esophagus presenting at the Lahey Clinic Medical Center from January 1973 to January 1989 were reviewed. During this period, 241 patients with documented Barrett's esophagus were seen, for a prevalence of carcinoma of 27%. Adenocarcinoma in Barrett's esophagus accounted for 30% of the surgically treated carcinomas of the thoracic esophagus during this period. All but four of these patients were men. Symptoms of chronic reflux were present in less than one half of the patients and dysphagia was often the presenting symptom. In eight patients the carcinoma was discovered on routine surveillance endoscopy, and in four patients progression of disease from benign columnar epithelium to dysplasia to carcinoma was documented. Tumors developed in six patients who had undergone previous antireflux surgery, and in four other patients a second carcinoma developed in residual Barrett's epithelium after a previous resection. Of the 65 patients, 61 (94%) were considered to have operable disease, all of whom underwent resection. Two patients (3.3%) died within 30 days of operation. The resected specimens were staged as follows: stage 0, 4; stage I, 10; stage II, 17; stage III, 25; stage IV, 4. Of the resected specimens, 73% showed areas of dysplasia adjacent to the tumor. The overall adjusted actuarial 5-year survival rate was 23.7%. The 3-year survival rate was 100% for patients with stage 0 carcinoma, 85.7% for patients with stage I carcinoma, 53.6% for patients with stage IIA carcinoma, 45% for patients with stage IIB carcinoma, 25.2% for patients with stage III carcinoma, and 0% for patients with stage IV carcinoma. The premalignant nature of Barrett's esophagus requires endoscopic surveillance to detect early carcinoma because symptoms often occur late or are absent. Antireflux surgery does not protect against the development of carcinoma. All of the Barrett's epithelium must be resected because a second carcinoma may develop in residual columnar epithelium. Severe dysplasia should be considered an indication for resection. Although operability and resectability rates are high, long-term survival is not. Early detection is mandatory if long-term survival is to be achieved.

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THE COLUMNAR EPITHELIUM-LINED lower esophagus, Barrett's esophagus, has been a source of controversy since its first description by Tileston in 1906[1] and its further definition by Barrett in 1950.[2] That it is an acquired condition caused by gastroesophageal reflux with malignant potential is accepted today. However the prevalence and incidence of malignant changes in Barrett's esophagus, the importance of associated mucosal dysplasia, and the long-term results of surgical therapy for these carcinomas are not understood fully. This review of our experience with adenocarcinoma in Barrett's esophagus was undertaken to clarify some of these issues by studying the clinical and pathologic features of the disease and the results of surgical therapy.

### *Definition*

Adenocarcinoma arising from Barrett's esophagus must be distinguished from carcinoma of the cardia arising in association with Barrett's esophagus. The former is defined as a malignant tumor, at least 75% of which lies within the tubular esophagus and which has adjacent benign columnar mucosa extending 3 cm or more above the gastroesophageal junction.

## Patients and Methods

The records of all patients with adenocarcinoma arising in Barrett's esophagus seen at the Lahey Clinic Medical Center from January 1973 to January 1989 were reviewed. In that period, 241 patients with Barrett's esophagus were seen, for a prevalence of carcinoma of 27% (Williamson WA, et al. Presented at the Fourth World Congress of the International Society for Diseases of the Esophagus, September 1989. Unpublished data). Findings from 65 patients form the basis of this report. These 65 patients accounted for 30% of the surgically treated carcinomas of the thoracic esophagus seen during that time.

All but four patients were men, and all were white. The median age of the patients was 60 years (range, 44 to 79 years). Neither heavy smoking nor alcohol consumption was a predominant clinical feature; only 38 (58%) of the group had a history of smoking cigarettes of more than 10 pack-years, and 14 patients had never smoked. Only

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15 patients had a history of heavy alcohol consumption.

The most common presenting complaint was dysphagia, which occurred in 43 patients and usually was present for less than 3 months. Hemorrhage, either upper gastrointestinal tract bleeding or anemia, was the presenting feature in eight patients, and odynophagia was the primary complaint in seven patients. Symptoms of chronic reflux or heartburn were present in 25 patients (38%), usually for longer than 10 years and, in most instances, were not the chief complaint.

Nine of the patients were known to have had Barrett's esophagus before the development of carcinoma, which was discovered on surveillance endoscopy. Progression of disease, from benign columnar mucosa to dysplasia to carcinoma was documented in four of these patients, and the disease in another patient who had severe dysplasia when first seen progressed to carcinoma. In four patients, second carcinomas developed in residual columnar epithelium after previous resection for a carcinoma in Barrett's esophagus. (Data on three of these patients, whose primary resections were performed elsewhere, were excluded from the survival calculations.) Six patients had undergone antireflux surgery (three of the operations were performed by us) an average of 7.8 years before the development of carcinoma. Nissen fundoplication was performed in four patients, Collis–Nissen operation was performed in one patient, and Collis–Belsey operation was performed in one patient.

### *Pathology*

The tumors were located in the lower esophagus in 54 patients and in the upper esophagus in 11 patients. Hiatal hernias were present in 31 patients.

Resected specimens were staged according to criteria in the *Manual for Staging of Cancer*[3]: stage 0, 4; stage I, 10; stage IIA, 8; stage IIB, 9; stage III, 25; stage IV, 4. Dysplasia of varying degrees was noted in association with tumors in 44 (73%) of the patients. The four patients with stage 0 carcinoma were operated on because of biopsies that showed carcinoma *in situ*, but in two of these patients the resected specimen showed only severe dysplasia. No patient was operated on because of a diagnosis of severe dysplasia only.

### *Surgery*

Of the 65 patients, 61 (93.8%) had disease that was considered operable, all of whom underwent resection, which was performed through the left chest in 19 patients, the abdomen and right chest (Ivor Lewis) in 24 patients, and by the transhiatal approach in 17 patients. (Data on one of these patients, diagnosed by us but operated on elsewhere, were excluded from the surgical statistics.) The stomach was used as an esophageal replacement in 54 patients, the colon in 5 patients, and in 1 patient the esophagus could not be reconstructed after resection because of previous gastric resection and chronic pancreatitis that caused severe mesenteric shortening, precluding bowel interposition.

### Results

Two patients died within 30 days of operation (hospital mortality rate, 3.3%): one patient died of a myocardial infarction, and the other patient died of pulmonary emboli. Complications occurred in 13 patients, including gastric outlet obstruction requiring operation in 3 patients, intra-abdominal abscess in 2 patients, cervical anastomotic leakage in 2 patients, and torsion of the intrathoracic stomach in 2 patients. Cerebrovascular accident, hemorrhage from splenic injury, deep venous thrombosis, and a contained intrathoracic leakage, which was treated conservatively, each occurred once. Postoperative functional results were excellent or good in 41 patients (68%), fair in 6 patients (10%), and poor in 13 patients (22%).

Adjusted survival curves were calculated by the Kaplan–Meier product limit method using the BMDP1L program. Statistical significance of differences between survival distributions was calculated by the Tarone–Ware method. The overall 5-year survival rate was 23.7% (Fig. 1). Comparison of survival by stage is shown in Figure 2. When the patients were subdivided by stage, the numbers were small, and meaningful data at the 5-year level were available only for patients in stages I, IIA, and IV. The 3-year survival rate was 100% for patients with stage 0 carcinoma, 85.7% for patients with stage I carcinoma, 53.6% for patients with stage IIA carcinoma, 45% for patients with stage IIB carcinoma, 25.2% for patients with stage

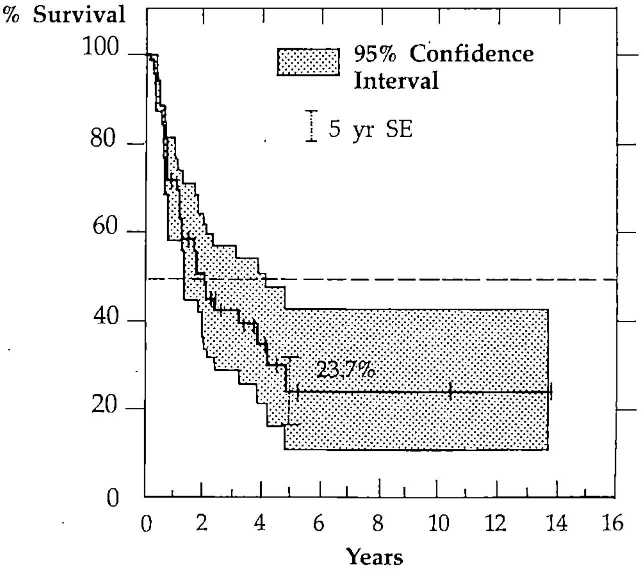

FIG. 1. Overall adjusted survival rate. Percentage and standard error of 5-year survival rate are shown. Vertical marks indicate censored patient withdrawal.

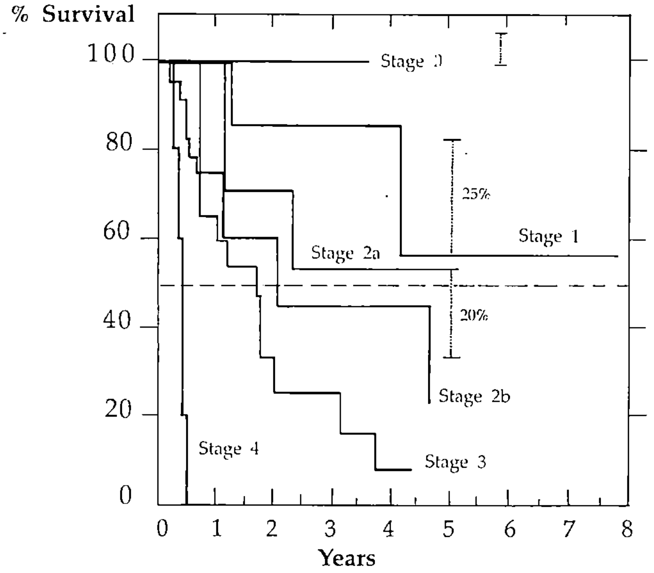

FIG. 2. Adjusted survival rate by stage. Percentage and standard error of available 5-year survival data are shown.

III carcinoma, and 0% for patients with stage IV carcinoma.

A comparison of 5-year survival rates for Barrett's esophagus, carcinoma of the cardia, and squamous cell epithelioma of the esophagus is depicted in Figure 3. The differences were not significant statistically. However when all patients, including patients not operated on as well as patients who died in the hospital, are considered, a better prognosis is suggested for patients with adenocarcinoma in Barrett's esophagus than for patients with squamous cell carcinoma because of the high operability and resectability rates and the low hospital mortality rate (Fig. 4). In multivariate analysis by the Cox proportional hazards method (BMDP2L), only stage was shown to be a significant independent predictor of survival. The type of operation performed did not significantly affect survival.

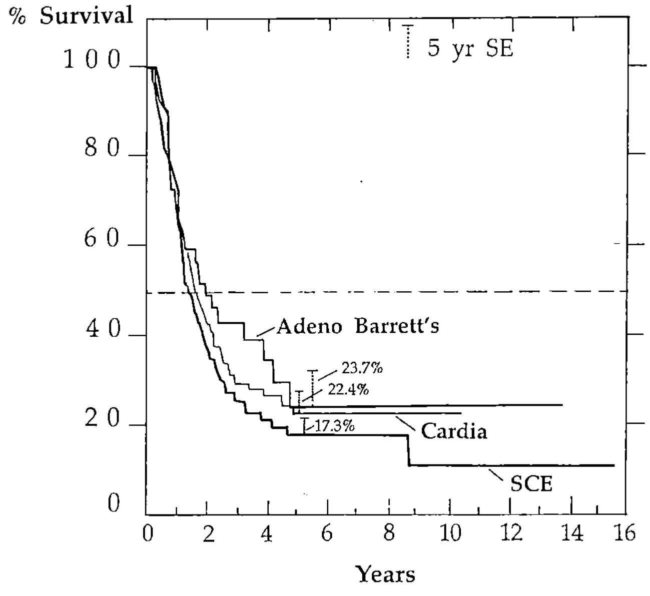

FIG. 3. Comparison of adjusted survival rate in patients with adenocarcinoma in Barrett's esophagus, carcinoma of the cardia, and squamous cell carcinoma of the esophagus (SCE).

## Discussion

Whether adenocarcinoma in Barrett's esophagus is being recognized more frequently than heretofore or whether the incidence truly is increased is unclear. What is certain is that adenocarcinoma in Barrett's esophagus comprises a significant percentage of thoracic esophageal carcinomas, 30% in our series and 41% in another report.[4]

Given the pathogenesis of the disease, it is surprising that more patients do not have a history of symptoms of chronic gastroesophageal reflux; only 38% of patients in our series and from 48% to 65% of patients in other series[5-8] report such symptoms. This finding is best explained by the proved decreased acid sensitivity of Barrett's epithelium (Ball CS, Watson A. Presented at the Fourth World Congress of the International Society for Diseases of the Esophagus, September 1989. Unpublished data). That antireflux surgery is no safeguard against the development of adenocarcinoma is shown by our six patients and by other reports.[4,8-11] We reserve antireflux surgery for patients with Barrett's esophagus who have complications of gastroesophageal reflux or intractable symptoms and do not use it to prevent the development of carcinoma.

The most common presenting symptom of Barrett's esophagus is dysphagia,[5,7,8,12] corresponding to the often advanced state of the disease when first diagnosed. Even so the operability and resectability rates in our patients were high, 93.8% and 100%, respectively, a feature of the disease noted by Sanfey et al.[8] and Lerut et al. (Presented at the Fourth World Congress of the International Society for Diseases of the Esophagus, September 1989. Unpublished data).

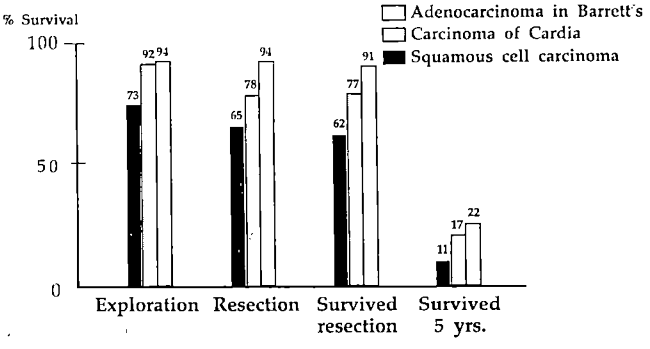

FIG. 4. Comparison of category survival rate (numbers show percentage survival rate).

The frequent association of dysplasia with adenocarcinoma in resected specimens in our patients and in reports by other workers[5–7,13–15] and the documented progression from benign to dysplastic to malignant epithelium emphasize the need for frequent surveillance and for esophageal resection when high-grade dysplasia is diagnosed. Resection can be performed with low morbidity and mortality and should encompass all columnar epithelium to eliminate the risk of the development of a second carcinoma.

In our experience and in that of others,[7] the survival rate after resection for patients with carcinoma and Barrett's esophagus is not different from that of patients with carcinoma of the cardia or squamous cell carcinoma of the esophagus. However one recent series (Lerut T, et al. Presented at the Fourth World Congress of the International Society for Diseases of the Esophagus, September 1989. Unpublished data) in which most of the patients underwent screening endoscopy reported a 55% overall 5-year survival rate, confirming the value of frequent surveillance and detection at an early stage. Only early diagnosis will improve long-term survival in patients with this disease.

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## References

1. Tileston W. Peptic ulcer of the oesophagus. Am J Med Sci 1906; 132:240–265.
2. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. Br J Surg 1950; 38:175–182.
3. Beahrs OH, Henson DE, Hutter RVP, et al, eds. Manual for Staging of Cancer. American Joint Committee on Cancer, 3rd Edition. Philadelphia: JB Lippincott, 1988.
4. Kuster GR, Foroozan P. Early diagnosis of adenocarcinoma developing in Barrett's esophagus. Arch Surg 1989; 124:925–928.
5. Harle IA, Finley RJ, Belsheim M, et al. Management of adenocarcinoma in a columnar-lined esophagus. Ann Thorac Surg 1985; 40:330–336.
6. Payne WS, Mcafee M, Trastek V, et al. Adenocarcinoma of the columnar epithelial-lined lower esophagus of Barrett. *In* Delarue NC, Wilkins E, Wong J, eds. International Trends in General Thoracic Surgery, Vol. 4. Esophageal Cancer. St. Louis: CV Mosby, 1988; pp 256–261.
7. Skinner DB, Walther BC, Riddell RH, et al. Barrett's esophagus: comparison of benign and malignant cases. Ann Surg 1983; 198: 554–565.
8. Sanfey H, Hamilton SR, Smith RR, Cameron J. Carcinoma arising in Barrett's esophagus. Surg Gynecol Obstet 1985; 161:570–574.
9. Hamilton SR, Hutcheon DF, Ravich WJ, et al. Adenocarcinoma in Barrett's esophagus after elimination of gastroesophageal reflux. Gastroenterology 1984; 86:356–360.
10. Naef AP, Savary M, Ozzello L. Columnar-lined lower esophagus: an acquired lesion with malignant predisposition. J Thorac Cardiovasc Surg 1975; 70:826–835.
11. Williamson WA, Ellis FH Jr, Gibb SP, et al. The effect of antireflux surgery on Barrett's mucosa. Ann Thorac Surg 1990; 49:537–542.
12. Sarr MG, Hamilton SR, Marrone GC, Cameron J. Barrett's esophagus: its prevalence and association with adenocarcinoma in patients with symptoms of gastroesophageal reflux. Am J Surg 1985; 149:187–193.
13. Saubier EC, Gouillat C, Samaniego C, et al. Adenocarcinoma in columnar-lined Barrett's esophagus: analysis of 13 esophagectomies. Am J Surg 1985; 150:365–369.
14. Hamilton SR, Smith RR. The relationship between columnar epithelial dysplasia and invasive adenocarcinoma arising in Barrett's esophagus. Am J Clin Pathol 1987; 87:301–312.
15. Haggitt RC, Tryzelaar J, Ellis FH Jr, Colcher H. Adenocarcinoma complicating columnar epithelial-lined (Barrett's) esophagus. Am J Clin Pathol 1978; 70:1–5.

# Mastectomy Following Preoperative Chemotherapy

## *Strict Operative Criteria Control Operative Morbidity*

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**The surgical morbidity associated with aggressive preoperative chemotherapy in 106 patients with advanced primary breast cancer who had chemotherapy followed by mastectomy was examined. These patients were compared with a group of 91 consecutive patients who had mastectomy without preoperative chemotherapy. Strict operative criteria were used to determine the timing of mastectomy following chemotherapy. Wound infection rates were no different in the preoperative chemotherapy group compared to the mastectomy-alone groups (7% *versus* 4%; p = 0.62). The incidence of wound necrosis was similar (11% *versus* 6%; p = 0.29). Seroma formation was decreased significantly in the preoperative chemotherapy group compared to the mastectomy-alone group (15% *versus* 28%; p = 0.04). Intensive preoperative chemotherapy did not delay the reinstitution of postoperative treatment (30% *versus* 20%; p = 0.27). However, when delay in instituting postoperative chemotherapy was more than 30 days, there was a significant decrease in overall survival rate (p = 0.04). This study provides evidence that intensive preoperative chemotherapy and mastectomy can be performed without increased morbidity. Furthermore it is important to institute systemic chemotherapy within 30 days of mastectomy to achieve maximum survival.**

IN THE PAST three decades progress in the treatment of patients with breast cancer has been marked by an expanding role of aggressive chemotherapy. Currently postoperative chemotherapy or hormonal therapy is the standard treatment for women who have breast cancer metastatic to the axillary lymph nodes.[1] Recent controlled trials indicate that adjuvant treatment also may benefit some subsets of breast cancer patients who have no nodal metastases.[2-4] Preoperative combination chemotherapy has been shown to improve the survival of patients with advanced primary breast cancer and inflammatory breast cancer.[5-7] The recent introduction of trials examining preoperative (neoadjuvant) chemotherapy in patients with less-advanced breast cancer[8] highlights the expanding role of chemotherapy in the treatment of patients with breast cancer. With the increasing use of perioperative chemotherapy, it is important to know that this treatment can be given safely without increasing the morbidity of mastectomy or delaying further therapy.

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In 1974 a strategy of giving preoperative chemotherapy was begun for patients with locally advanced primary breast cancer (stage III) at the University of Texas M.D. Anderson Cancer Center. Overall response rates exceeded 90%, and most of these patients had mastectomy following chemotherapy. We reviewed our experience with preoperative chemotherapy for locally advanced breast cancer, testing the hypothesis that aggressive preoperative chemotherapy and mastectomy would not adversely affect postoperative recovery compared to patients having a mastectomy alone when examining the endpoints of wound infection, wound necrosis, seroma, and delay in resuming postoperative therapy. In addition we examined whether a delay in resuming chemotherapy following mastectomy adversely affected survival rate.

### Patients and Methods

The hospital records of 106 patients who presented with advanced breast cancer were reviewed. Patients were clinically staged to have either T3, T4, and/or N2, N3 breast cancer using the 1983 American Joint Committee on Cancer criteria.[9] All patients initially were evaluated in a multidisciplinary breast clinic where surgical oncologists, medical oncologists, and radiotherapists were present. All patients were enrolled in a protocol between 1974 and 1985 and received preoperative chemotherapy followed by total mastectomy with axillary dissection.

The preoperative chemotherapy has been described[5] and consisted of 500 mg/m$^2$ 5-fluorouracil administered intravenously on days 1 and 8, 500 mg/m$^2$ doxorubicin administered intravenously on day 1, and 50 mg/m$^2$ cyclophosphamide given intravenously on day 1. Following three to six 21-day cycles of chemotherapy, a total mastectomy and axillary dissection was performed. After operation patients resumed chemotherapy for 6 to 18 months. External beam radiotherapy was given at the completion of postoperative chemotherapy.

These patients were compared to a group of 91 patients with breast cancer who had mastectomy without preop-

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erative chemotherapy (mastectomy-alone group) at our institution in 1985. The two groups were analyzed for the following endpoints: (1) wound infection, (2) wound necrosis, (3) seroma, and (4) delay in resuming postoperative chemotherapy.

Strict operative criteria were used to plan the timing of surgery after preoperative chemotherapy. All patients were examined by the surgeon after the completion of chemotherapy and determined to be resectable. If unresectable radiotherapy was given before surgery, laboratory examination was performed, and patients were required to have a white blood cell count (WBC) of more than than 2500 cells/mm$^3$ and a platelet count of more than than 50,000 cells/mm$^3$. These criteria avoided the chemotherapy nadir. The operative surgeons and technique were the same in both groups. Demographic data included age, clinical stage of disease, tumor size, and lymph node status. Additional information obtained in the preoperative chemotherapy patients included number of courses of chemotherapy, complications of chemotherapy, WBC count, platelet count, hematocrit level, length of time after the last chemotherapy dose, surgeon, number of lymph nodes removed, number of lymph nodes involved with tumor, operative procedure, recurrence, and survival. Complications analyzed included wound infection, wound necrosis, seroma, and delay in resuming chemotherapy. Wound infection was defined as clinical signs of infection requiring antimicrobial therapy. Wound necrosis was defined as any skin loss requiring therapeutic intervention (*i.e.*, antibiotic administration, debridement, or dressing changes). Seroma was defined as any fluid collection requiring aspiration from the axilla or chest wall. Delay in resuming chemotherapy was defined as treatment that was begun more than 30 days after mastectomy.

Data was analyzed with the D-Base III-Plus® program (Ashton-Tate, Culver City, CA) using a personal computer. Statistical analysis was performed with AbStat® (Anderson-Bell, Parker, CO). Significant differences between groups were analyzed by chi square, and significance was assumed if $p < 0.05$. Survival curves were calculated and plotted using the Kaplan–Meier method,[10] and the generalized Wilcoxon test was used to test differences in survival.[11]

The following null hypotheses were tested.

(1) There is no significant difference in surgical morbidity (wound infection, wound necrosis, seroma, and delay in resuming chemotherapy) in preoperative chemotherapy patients compared to patients who had mastectomy without preoperative chemotherapy.

(2) There is no significant difference in survival of patients treated with preoperative chemotherapy who have delay in resuming chemotherapy after mastectomy compared to patients who do not have a delay in resuming chemotherapy.

## Results

There were 106 patients in the preoperative chemotherapy group and 98 patients in the mastectomy-alone group. The average age was 50.1 years (range, 20 to 76 years) in the preoperative chemotherapy group and 55.2 years (range, 31 to 96 years) in the mastectomy-alone group. Tumor stage in the preoperative chemotherapy group was I (0%), II (1%), IIIA (29%), IIIB (66%), IV (2%), and bilateral (2%). Patients in the mastectomy-alone group had the following stage: I (53%), II (44%), IIIA (1%), IIIB (0%), IV (1%), and bilateral (1%).

### *Preoperative Chemotherapy*

Patients who had preoperative chemotherapy had a median of three courses of treatment (range, 2 to 21 courses). The overall response rate was 90%. Six patients had a complete response (5.7%), and 90 patients had a partial response (84.9%). Seven patients had no response (6.6%), and two patients progressed while on treatment (1.9%) Response could not be determined for one patient by a review of the chart. Ninety-one patients (85.8%) had no complications related to their chemotherapy before surgery, and only four patients (3.8%) were thought to have had their surgery delayed by a complication of chemotherapy. One patient required preoperative radiation therapy; she had no response to preoperative chemotherapy and was not surgically resectable. She had no postoperative complications.

Patients had mastectomy a median of 27 days after their last chemotherapy course (range, 6 to 108 days). Two patients had a significant delay in surgery after preoperative chemotherapy (381 and 526 days) and were excluded from analysis. The median WBC count was 5.2 cells/mm$^3$ (range, 1.7–13.6 cells/mm$^3$), and the median platelet count was 293,000 cells/mm$^3$ (range, 3.67 to 636,000 cells/mm$^3$). Six patients had a WBC count of less than 2500 cells/mm$^3$,and one patient had a platelet count of less than 50,000 cells/mm$^3$. Our criteria for the timing of mastectomy were followed in 100 patients (94%).

### *Surgery and Surgical Morbidity*

The following procedures were performed in the preoperative chemotherapy group: extended simple mastectomy (mastectomy and level I axillary dissection), 72%; modified radical mastectomy, 12%; simple mastectomy, 9%; bilateral mastectomy, 6%; and segmental mastectomy, 1%. The following procedures were performed in the mastectomy-alone group: extended simple mastectomy, 11%; modified radical mastectomy, 61%; simple mastectomy, 1%; bilateral mastectomy, 8%; and segmental mastectomy, 18%. The average number of lymph nodes re-

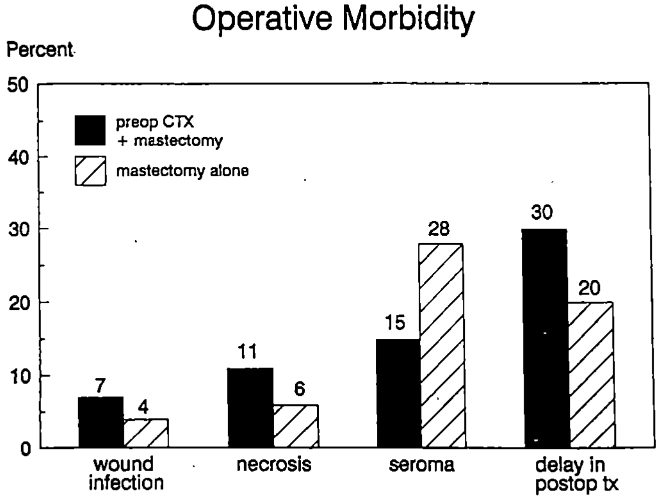

FIG. 1. Surgical morbidity preoperative chemotherapy + mastectomy patients *versus* mastectomy alone patients. No significant differences were noted with respect to wound infection (chi square, p = 0.62), wound necrosis (chi square, p = 0.29), and delay in postoperative treatment (chi square, p = 0.27). There was a significant difference in seroma formation (chi square, p = 0.04).

moved at surgery was similar in the two groups (13 *versus* 16).

Surgical morbidity is compared in Figure 1. There were no significant differences in wound infection, wound necrosis, or delay in resuming chemotherapy rates between the two groups. There was a significant difference in seroma rates between the two groups (15% *versus* 28%; p = 0.04).

In the preoperative chemotherapy group, chemotherapy was resumed a median of 27 days after mastectomy discharge (range, 0 to 1478 days). Two patients did not have chemotherapy after surgery (1.9%), and three patients had chemotherapy reinstituted more than 2 years after surgery (2.8%). They were excluded from the survival analysis. Seven patients had chemotherapy started within 14 days of mastectomy. There was one seroma in this group (14%). Forty-six patients in the mastectomy-alone group had chemotherapy after mastectomy (46.9%).

### *Effect of Delaying Postoperative Chemotherapy*

The survival of preoperative chemotherapy patients who had delay in resuming chemotherapy by more than 30 days following mastectomy was compared to those preoperative chemotherapy patients who had no delay (Fig. 2). Median survival was statistically worse in those patients who had delay compared to those who did not (median survival, 33.2 *versus* 56.1 months; p = 0.04). Overall median survival time was 54.3 months.

## Discussion

This study directly examined surgical morbidity in mastectomy patients following aggressive preoperative chemotherapy. Several other studies have examined surgical complications of chemotherapy following mastectomy. Cohn et al.[12] analyzed the surgical complications in the National Surgical Adjuvant Breast Project (NSABP). In this study patients who had 3 days of peri-

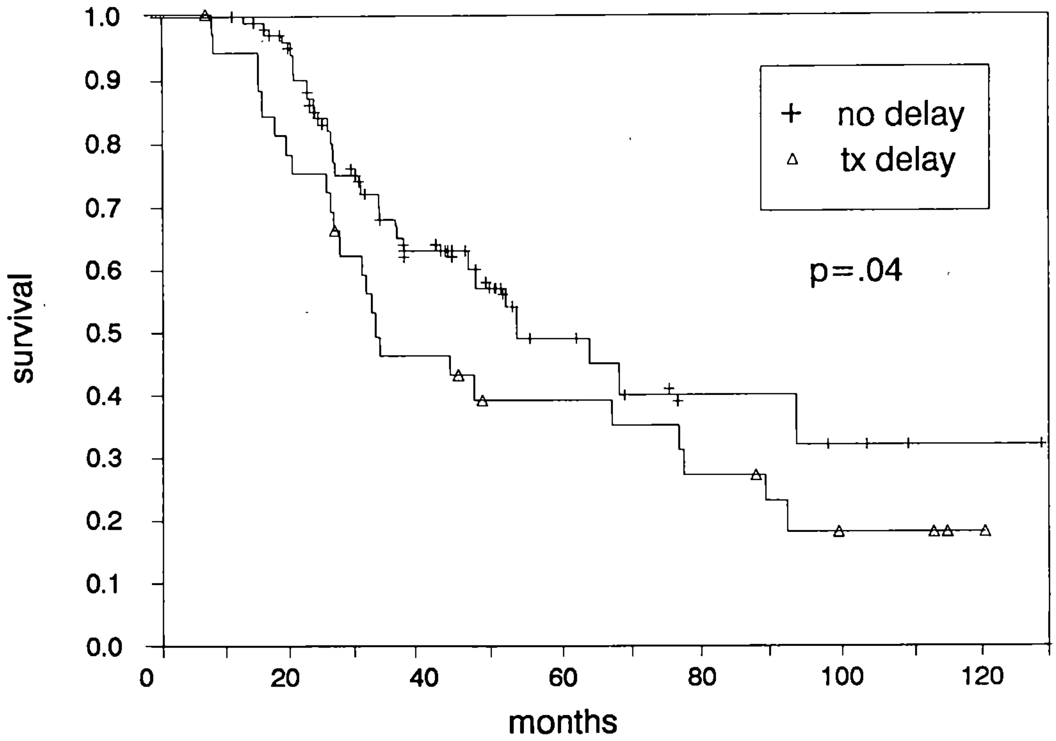

FIG. 2. Survival in advanced primary breast cancer patients grouped by delay *versus* no delay in resuming systemic therapy after mastectomy.

operative thio-tepa and mastectomy were compared to those who had placebo and mastectomy. They found that local complications in both groups were high, but no difference was found in the patients who had perioperative chemotherapy (47% *versus* 43%). Patients had wound infections regardless of whether chemotherapy was given (20% in either group). Knight et al.[13] discussed the surgical results of 18 patients with inflammatory cancer who were treated with preoperative chemotherapy and radiation, followed by mastectomy. They found wound problems in 7 of the 18 patients (39%). Three patients had wound infection (17%), two had seromas (11%), and one patient each had wound necrosis and erythema.

There have been several experimental studies that have examined the effect of chemotherapy on wound healing.[14–17] These studies resulted in conflicting data. Extrapolating the results of chemotherapy on wound healing in rats to humans is important in initial phases of research but has limited clinical value. Our analysis concludes that the rate of complications of mastectomy following preoperative chemotherapy is not significantly different than the morbidity of surgery alone. No significant difference in wound infection, wound ischemia, or delay in instituting chemotherapy between the two groups was found. Interestingly the incidence of seroma formation was significantly decreased in patients who had preoperative chemotherapy. It will be interesting to see whether seroma rates are decreased in patients who receive preoperative chemotherapy in the NSABP B-18 clinical trial.

We developed simple guidelines to determine the timing of mastectomy after preoperative chemotherapy. These require that the patient be resectable without the need for skin grafting or reconstructive surgery and that the WBC and platelet count be adequate to minimize the risk of infection or bleeding. These criteria avoid the patient's chemotherapy nadir.

Our study demonstrated a significant reduction in survival in patients with advanced primary breast cancer who had systemic therapy delayed more than 30 days after mastectomy. While there was no statistical difference in the incidence of delaying postoperative therapy between the preoperative chemotherapy and mastectomy-alone groups, the incidence was high in both groups (30% *versus* 20%). These findings provide an argument for designing strategies that resume systemic treatment early after mastectomy.

The use of preoperative chemotherapy in patients with advanced primary breast cancer has been a major advance. Patient survival has been improved, and the high response rates have allowed for mastectomy without the need for more extensive surgical procedures. This study shows that strict operative criteria that determine the timing of surgery allow mastectomy without increasing surgical complication rates.

## References

1. Glick JH. Meeting highlights: adjuvant therapy for breast cancer. J Natl Cancer Inst 1988; 80:471–475.
2. Fisher B, Redmond C, Dimitrov NV, et al. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node negative breast cancer who have estrogen receptor negative tumors. N Engl J Med 1989; 320:473–478.
3. Mansour EG, Gray R, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high risk node negative breast cancer. N Engl J Med 1989; 320:485–490.
4. Balch CM, Singletary SE. Adjuvant therapy for node-negative breast cancer patients. Who benefits? Arch Surg 1988; 123:1189–1190.
5. Hortobagyi GN, Ames FC, Buzdar AU, et al. Management of stage III primary breast cancer with primary chemotherapy, surgery, and radiation therapy. Cancer 1988; 62:2507–2516.
6. Piccart MJ, deValeriola D, Paridaens R, et al. Six-year results of a multimodality treatment strategy for locally advanced breast cancer. Cancer 1988; 62:2501–2506.
7. Hobar PC, Jones RC, Schouten J, et al. Multimodality treatment of locally advanced breast cancer. Arch Surg 1988; 123:951–955.
8. Breast cancer protocol updates. NSABP Newsletter. September 1989, page 5.
9. American Joint Committee on Cancer. Breast. *In* Bearhs OH, Myers MH, eds. Manual for Staging of Cancer, Second Edition. Philadelphia: JB Lippincott, 1983; pp 127–133.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481.
11. Gehan EA. A generalized Wicoxon test for comparing arbitrarily singly censored samples. Biometrics 1965; 52:203–223.
12. Cohn I, Slack NH, Fisher B. Complications and toxic manifestations of surgical adjuvant chemotherapy for breast cancer. Surg Gynecol Obstet 1968; 127:1201–1209.
13. Knight CD, Martin JK, Welch JS, et al. Surgical considerations after chemotherapy and radiation therapy for inflammatory breast cancer. Surgery 1986; 99:385–390.
14. McGonigal MD, Martin DM, Lucas CE, et al. The effects of breast cancer chemotherapy on wound healing in the rat. J Surg Res 1987; 42:560–564.
15. Bland KI, Palin WE, von Fraunhofer JA, et al. Experimental and clinical observations of the effects of cytotoxic chemotherapeutic drugs on wound healing. Ann Surg 1984; 199:782–790.
16. Shamberger R. Effect of chemotherapy and radiotherapy on wound healing. Recent Results in Cancer Research 1985; 98:17–34.
17. Raaf JH. Techniques for avoiding surgical complications in chemotherapy treated cancer patients. Recent Results in Cancer Research 1985; 98:46–52.

# Clinical Outcome of Seriously Ill Surgical Patients with Intra-abdominal Infection Depends on Both Physiologic (APACHE II Score) and Immunologic (DTH Score) Alterations

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**The delayed-type hypersensitivity (DTH) response and the APACHE II score in 118 patients with surgical infections were measured prospectively and related to outcome. Logistic regression analysis generated the equation:**

$$p|\text{death}| = \frac{\exp[-4.062 + 0.132(\text{APACHE II}) - 0.371 * \ln(\text{DTH score})]}{1 + \exp[-4.062 + 0.132(\text{APACHE II}) - 0.371 * \ln(\text{DTH score})]}$$

**The risk assessment as calculated by this model was compared to that using the APACHE II system alone in a separate group of 354 patients. There was an improvement in the predictive capacity of the APACHE II + DTH equation compared to APACHE II alone, as shown by a better fit of expected and observed deaths, an improved Goodman–Kruskal G statistic, and a larger area under the receiver operating characteristic curve. It is concluded that the DTH response (a broad marker of immunocompetence) is an independent prognostic factor in surgical patients and can be used in combination with the APACHE II score (a measure of acute physiology) to estimate better the outcome of surgical patients.**

OUTCOME PREDICTION IS important in the disease stratification and subsequent decision-making process in the acutely ill surgical patient. A proposed stratification system is the APACHE II, which generates a point score based on 12 physiologic variables, age, and previous health status.[1] This score has been used successfully in the assessment of patients admitted to an intensive care unit (ICU). No such data exist for patients with serious intra-abdominal infections. Intuitively one would also expect the immunologic defense apparatus to alter final outcome, especially in patients with infections. An impaired delayed-type hypersensitivity (DTH) skin-test response to recall antigens is associated with an increase rate of death in surgical patients.[2] Studies using logistic regression analysis in a mixed patient population showed that the patient's skin-test score, serum albumin, age, and sex significantly and independently contributed to the probability of death calculation.[3]

In this study we examined whether the DTH skin-test score, a reliable marker of host defense capability, could be combined with the APACHE II score to provide a better estimate of outcome in surgical patients.

## Materials and Methods

### Patient Population

*Group 1 (training set).* One hundred eighteen patients admitted to the surgical wards and/or the surgical intensive care unit (SICU) of the Royal Victoria Hospital, Department of Surgery, McGill University, Montreal, Canada were entered prospectively into the study. Included were consecutive emergency admissions clinically suspected of having intra-abdominal sepsis. Patients with infections were chosen as the 'training set' to maximize the contribution, if any, of the altered host defense mechanisms. Exclusion criteria were recent radiotherapy, chemotherapy, or treatment with corticosteroids. All patients were assessed within 24 hours of admission.

*Group 2 (validation set).* A group of patients that is different from the one used to generate the model is required to validate the analysis. Data from 354 prospectively studied surgical admissions were used for this purpose. Patients with varying surgical conditions, including infections, were selected for use. They had both a DTH and an APACHE II score, as well as all the other independent variables, measured within 24 hours of their admission. Exclusion criteria were recent radiotherapy, chemotherapy, or treatment with corticosteroids. We chose a mixed patient population, which included those diagnosed as having intra-abdominal infections as well as other surgical conditions, to determine the applicability of the model to a wider range of surgical pathology.

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### *DTH Skin Testing*

Delayed-type hypersensitivity skin tests were performed with five recall antigens using the upper arm or the volar surface of the forearm. The antigens were *Candida* (Candidin 1:100 dilution), mumps skin-test antigen (undiluted), purified protein derivative (5TU), trichophytin and streptokinase-streptodornase (Varidase,™ 100 units/mL; Varidase™ is not available on the market at this time), in 0.1-mL volumes injected intradermally. The indurated area, rather than the surrounding erythema, was measured at 24 and 48 hours. The largest and smallest diameters for each antigen were used to compute an average response for each antigen. For example, if Varidase caused a 3 × 4-mm reaction, this was scored as a 3.5-mm response. In 90% of the cases the 24-hour reading was used. The final DTH score was defined as the sum of the individual antigen responses. Alternatively an antigen response was defined as positive if the mean diameter of the induration for that antigen was equal to or greater than 5 mm. Subjects then were classified as reactive if they had two or more positive responses, relatively anergic if they had one antigen response, and anergic if they demonstrated no response to any antigen. No skin or blood testing was carried out in the first 24 hours after surgery to avoid a possible anesthetic effect on these measurements. Hematologic and biochemical tests were performed in the hospital laboratory as per protocol.

### *Additional Data Collection*

All patients had the following data recorded: sex, age, APACHE II score (using the ICU Research Unit APACHE II scoring sheets), diagnosis, past medical history, serum albumin, all surgical interventions with timing, type, and contamination status, postoperative complications, and final hospital outcome. Deaths were considered septic-related if on the autopsy report, or on the death certificate if no autopsy was done, infection was the stated cause of death or contributed to the death. A history-based assessment of the state of the host-defense mechanism also was obtained. Any patient with a history of neoplasia, corticosteroid intake, or other conditions likely to cause immunodepression was scored as being clinically immunodepressed.

### *Statistical Analysis*

Stepwise forward logistic regression analysis was used to obtain estimates of the risk of death. The logistic function has the form

$$p\,|\,\text{outcome} = \text{death}\,|$$

$$= \frac{\exp(-b_0 - b_1x_1 - \cdots b_kx_k)}{1 + \exp(-b_0 - b_1x_1 - \cdots b_kx_k)}$$

($p$ = probability; exp = natural logarithm; $b_0, b_1 \ldots b_k$ = coefficients to be estimated; $x_1, x_2 \ldots x_k$ = independent variables).[4] Starting with a constant model having $b_0$ as the only parameter, variables were entered into the equation only if their addition increased the likelihood of the model with a significant p value ($p < 0.05$) using two-tailed tests of significance.[4] Mortality was used as the dependent outcome variable. Independent variables examined were DTH and APACHE II scores, age, and albumin. This analysis was carried out with the BMDP Statistical Software[5] version 1988 (Los Angeles, CA) in consultation with the McGill Faculty of Epidemiology and Biostatistics.

The resulting equation was tested on the validation group as follows: patients were grouped into deciles of risk of death based on the probability obtained for each from our equation. The individual probabilities within each decile were summed to determine the number of expected deaths within that decile, which then was compared to the number of observed deaths. For example all 245 patients with a probability of death computed to be between 0 and 0.1 (*i.e.*, less than 10%) were grouped into the first probability decile. The sum of the individual probabilities of death in this group was 6.5—the expected number of deaths within the first decile. The observed number of deaths in this decile was 10, indicating a moderate fit of the model. Goodness of fit was assessed by chi square analysis, the Goodman–Kruskal G statistic,[6] and receiver operating characteristic (ROC) curve analysis[7] (ROCFIT program from the Franklin McLean Memorial Research Institute, University of Chicago). The G statistic, or gamma, is a correlation test for two variables with ordered categories and provides a measure of the monotone relationship, or probability of similar ranking, between the two variables. Its values range from −1 to +1, with values near +1 signifying a strong positive correlation, −1 signifying a strong negative correlation, and 0 signifying no correlation. Thus we were able to quantify the degree of similar ranking into deciles of the expected and observed deaths by our equation. Receiver-Operating-Characteristic curve analysis allowed us to plot the true-positive rate and the false-positive rate of our score because the cut-off point for the computed probability of death was varied systematically. By this means it was possible to calculate the area $A_z$ under the ROC curve, which is an indicator of the overall correct classification rate. $A_z$ ranges from 0.5 for chance performance to 1 for perfect prediction. Then we used the equation derived by Knaus et al.[1] in a similar fashion in the validation group to establish its goodness of fit by the same three tests. The areas under the two curves obtained by either model through ROC curve analysis were compared using the CORROC software program[8] (Franklin McLean Memorial Research Institute, University of Chicago). The program calculates the individual areas then provides the statistical significance of the difference between them by using a built-in 'area test.'

TABLE 1. *Admitting Diagnosis of the 118 Patients Used to Derive the Predictive Equation*

| Diagnosis | Number of Patients |
|---|---|
| Type of Infection | |
| Peritonitis | 52 |
| Intra-abdominal abscess | 51 |
| Other | 15 |
| Site of Infection | |
| Esophagus/stomach | 19 |
| Duodenum/small bowel | 8 |
| Colon/appendix | 72 |
| Pancreaticobiliary tract | 16 |
| Extremity | 3 |

TABLE 2. *Additional Data for the 118 Patients Used to Derive the Predictive Equation*

| Variable | Value (±SD) |
|---|---|
| Age (years) | 56.4 ± 17.9 |
| Sex | |
| Men | 65 |
| Women | 53 |
| Clinically immunodepressed (%) | 35 |
| Serum albumin (g/L) | 28.5 ± 7.3 |
| APACHE II score | 14.5 ± 9.1 |
| DTH score | 11.5 ± 15.6 |
| Deaths | 22 (18.6%) |

DTH, delayed-type hypersensitivity.

## Results

The 118 initial patients comprising the training set were entered into the study based on the diagnosis of a surgical infection. As shown in Table 1, most patients had peritonitis or intra-abdominal abscess, in equal distribution. A wide spectrum of surgical diseases were represented. The variables entered in the logistic regression analysis and some additional patient characteristics are shown in Table 2. The mean APACHE II score of 14.5 and mortality rate of 19% attests to the serious surgical illness of the training set. Within this group there were no significant differences in the DTH score among patients with various infection types or sites. Figure 1 depicts the effect on outcome of four patient variables: serum albumin, APACHE II score, DTH skin-test score, and host defense as derived from history. While all variables differ in those who survived compared to those who died, the result is particularly striking with the DTH skin-test score, which averages 12 in the patients who lived compared to 0 in the group of patients who died. In this same training set, Figure 2 displays the effect of host immune status on outcome by showing the major difference in mortality between DTH nonreactive and reactive patients, both from infectious causes and from all causes of death.

The logistic regression analysis is shown in Table 3. Only the APACHE II and DTH skin test scores contributed significantly and independently to the model. As expected age as an independent variable yielded no significant contribution to outcome prediction due to its inclusion in the APACHE II score. Albumin also was rejected, displaced in all likelihood by the APACHE II score.

Using the coefficients shown in Table 3, the equation to calculate the probability of death of a particular surgical patient admitted to hospital takes the form:

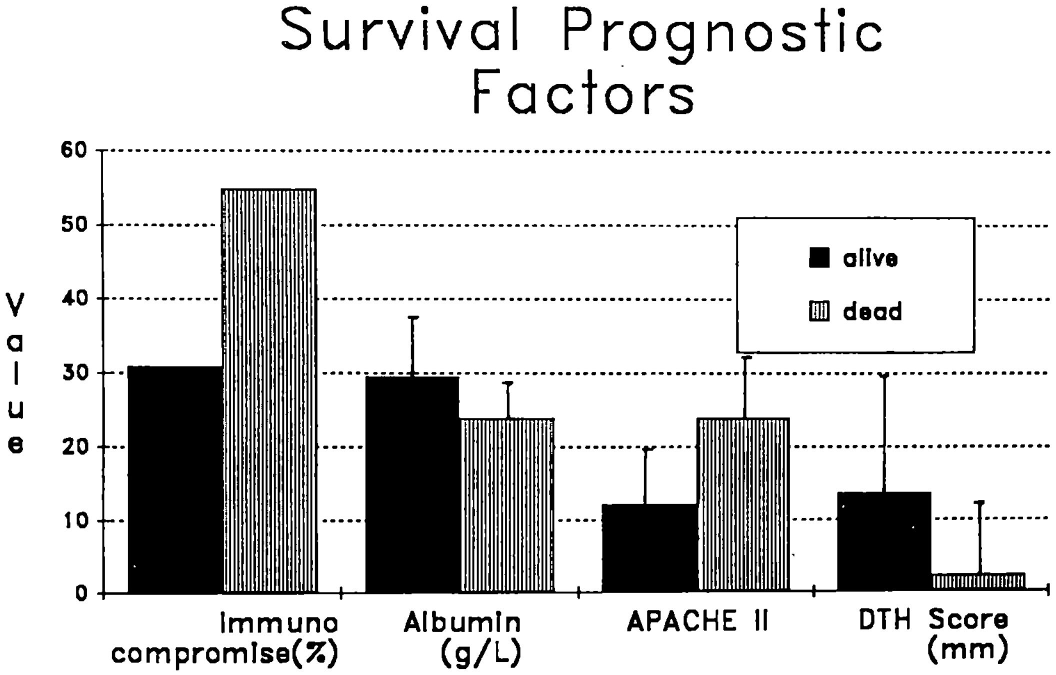

FIG. 1. Effect of four independent patient characteristics on overall mortality rate: percentage clinically immunocompromised patients and mean values for serum albumin, APACHE II score, and DTH skin test score for patients who were discharged alive *versus* those who died during the current admission.

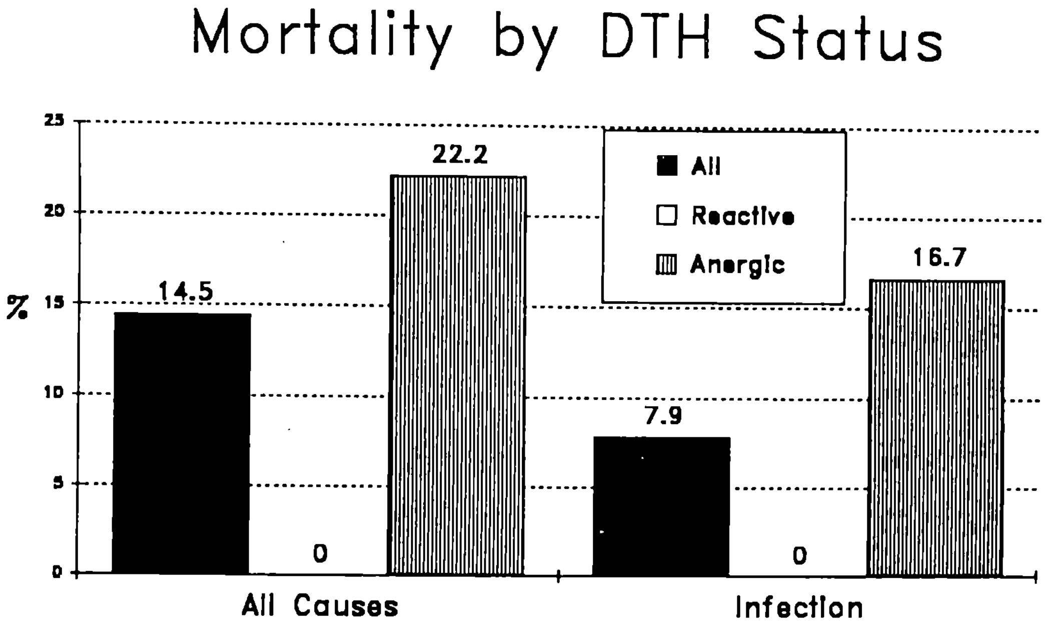

FIG. 2. Mortality rates from septic causes alone and from all causes according to the immune status of the patient.

$$p|\text{death}| = \exp(x)/[(1 + \exp(x)]$$

where $x = -4.062 + 0.132\,(\text{APACHE II}) - 0.371 * \ln(\text{DTH score})$.

Table 4 lists the admission diagnoses for the separate 354 patients who formed the validation set. Table 5 lists their additional data profile. It is apparent that this group is widely mixed, encompassing the entire span of surgical conditions. Trauma and intra-abdominal abscess cases had significantly lower mean DTH scores (9.4 and 8.8 mm, respectively) than did patients with peritonitis (15.6 mm), upper gastrointestinal bleeding (17.4 mm), and malignancy (19.6 mm). The mean APACHE II score was slightly lower compared to group 1, indicating 'less severe' physiologic alterations, *i.e.*, disease severity, in these patients.

The values for each validation patient's APACHE II score and logarithm of DTH score were entered in the predictive equation and a probability of death was calculated for each patient. The lowest probability was 0 and the highest was 0.96. The expected deaths then were calculated within each probability decile by adding the individual probabilities of the patients placed in that decile. In a similar fashion, death probabilities for the validation set were derived from the equation using the APACHE II score from Knaus[1]

$$p|\text{death}| = \exp(x)/[1 + \exp(x)],$$

$$\text{where } x = -3.517 + 0.146(\text{APACHE II}) + 0.06.$$

($*$ = mean diagnostic category weight for postemergency surgery for gastrointestinal perforation, bleeding, neoplasm, or for trauma) and expected deaths within each decile were computed.

Figure 3 shows the observed and expected deaths for all deciles using the APACHE II score alone, while Figure 4 presents the results of the combined DTH + APACHE II model. Table 6 lists the statistical results of the goodness-of-fit tests, and Figure 5 shows the ROC curves for both the training and the validation sets. The areas under each model were compared by the CORROC program and showed a statistically significant improvement in predictive power of the combined model in both patient groups with $p < 0.05$.

TABLE 3. *Final Logistic Regression Step in Derivation of Equation*

| Variable* | Coefficient | p value | Improvement $X^2$ |
|---|---|---|---|
| Intercept ($b_0$) | −4.062 | | |
| APACHE II score | 0.132 | 0.0026 | 24.8 |
| DTH skin test score | −0.371 | 0.0350 | 6.1 |

* Variables entered in the model only if $p < 0.05$.
DTH, delayed-type hypersensitivity.

TABLE 4. *Admitting Diagnosis of the 354 Patients Used to Test the Validity of the Equation*

| Diagnosis | Number |
|---|---|
| Gastrointestinal bleeding | 76 |
| Intra-abdominal sepsis | 69 |
| Trauma | 32 |
| Pancreaticobiliary tract disease | 22 |
| Cancer | |
| Stomach | 15 |
| Pancreaticobiliary | 23 |
| Colorectum | 68 |
| Other | 14 |
| Miscellaneous | 35 |

TABLE 5. *Additional Data for the 354 Patients Used to Test the Validity of the Equation*

| Variable | Value (±SD) |
|---|---|
| Age (years) | 60.2 ± 16.9 |
| Sex | |
| Men | 210 |
| Women | 145 |
| Serum albumin (g/L) | 32.5 ± 6.9 |
| APACHE II score | 12.6 ± 7.8 |
| DTH score | 17.7 ± 17.3 |
| Deaths | 40 (11.3%) |

DTH, delayed-type hypersensitivity.

## Discussion

The hypothesis that a group of selected physiologic variables can be used to predict the outcome of an acutely ill patient has been well demonstrated by the clinical value of the APACHE II score. Simplification of the classification system from the original 34 physiologic measurements[9] to the current 12 variables has made the test easier to perform without loss of its predictive power.[1] However the score is applicable only in the acute setting (mostly to medical ICU patients) for which it was designed. Furthermore prediction of individual death requires adjustments for each of 50 diagnostic categories. Finally the APACHE II test does not use an objective measure of host immunocompetence. Surgical patients have a high incidence of infectious complications, and thus the inclusion of host defense capability to any predictive model would seem desirable.

The outcome of a surgical population, comprising both acute and elective admissions, has been correlated repeatedly to the state of the patient's immunocompetence as measured by the DTH skin test response.[2,10] Further studies showed that DTH, serum albumin, and age were variables associated with the probability of death.[3,11]

Based on the premise that the two scoring systems measure two separate aspects of the patient's health, *i.e.*, the physiologic response to 'stress' and the immune defense status, we tried to combine these into a broader and more accurate predictive model. The success of each classification system in its own area of use has led to the hypothesis that a combined model would have an expanded spectrum of usefulness and result in a widely applicable, easily performed objective measurement of surgical risk in the seriously ill surgical patient.

The required logistic regression analysis using both APACHE II and DTH plus additional variables, such as albumin, was performed in a selected group of acute surgical admissions to ensure a wide distribution of DTH and APACHE II scores, as well as sufficient 'events,' *i.e.*, deaths, to make the study feasible in our center. The APACHE II score was the most significant variable related to death (improvement chi square = 24.8), demonstrating the importance that physiologic abnormalities play in the survival from sepsis. The DTH skin test score was the next most significant variable (improvement chi square = 6.1), again revealing the contribution of host defense to outcome independent of physiologic state. Neither age nor serum albumin level contributed significantly to the calculation of the probability of death in this analysis.

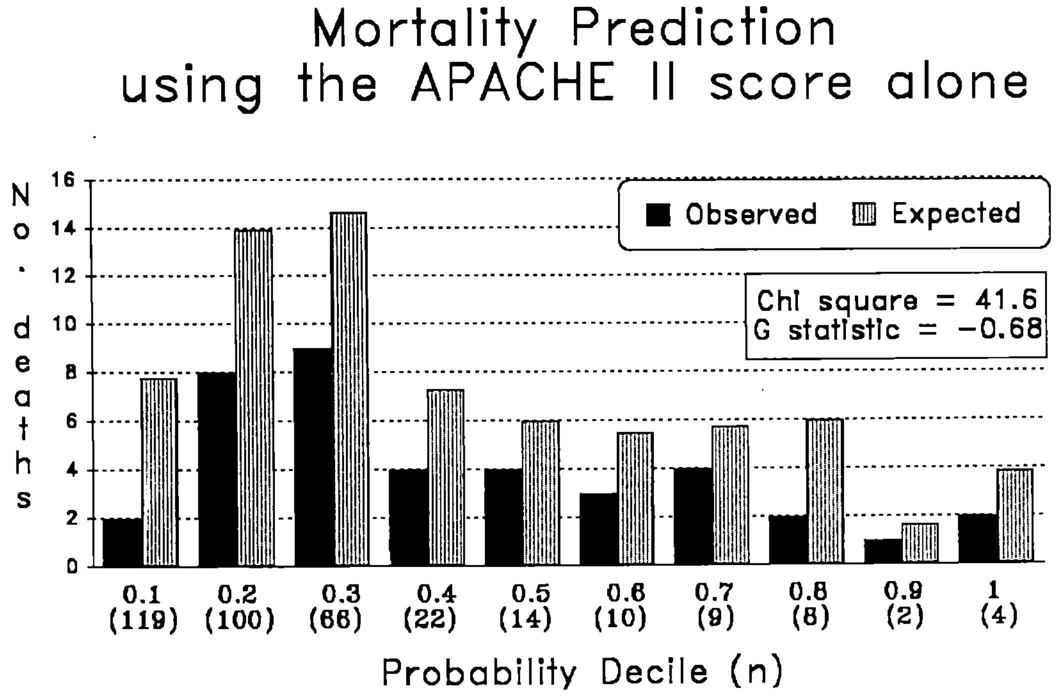

FIG. 3. Observed and predicted deaths by the APACHE II score alone in the 354 patients used to test the predictive model.

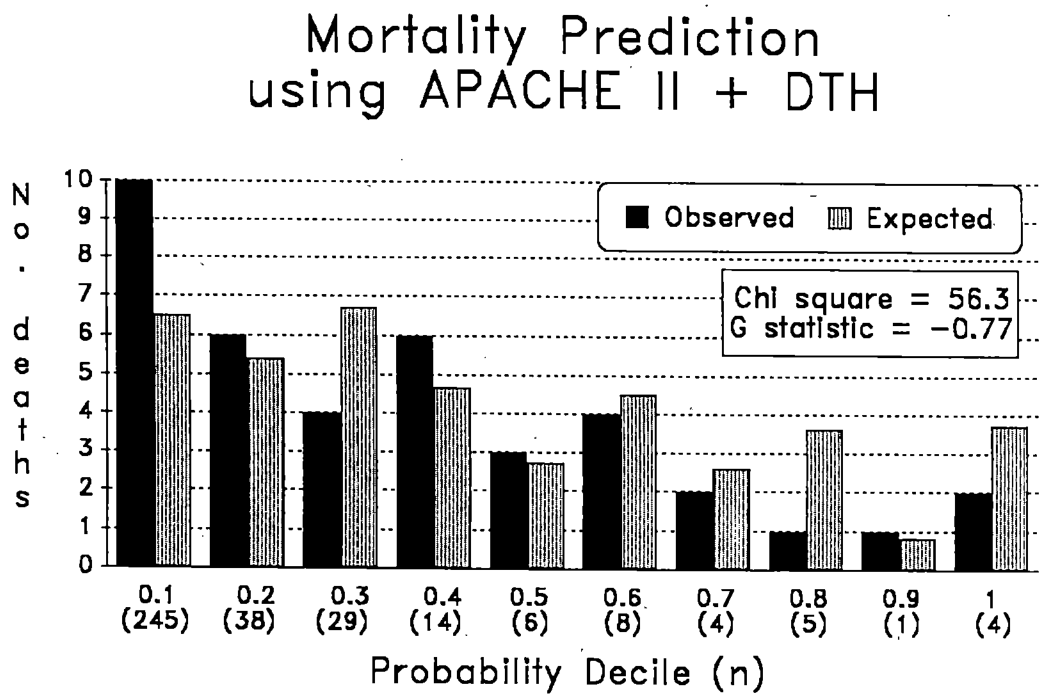

FIG. 4. Observed and predicted deaths by the APACHE II score in conjunction with the DTH score in the 354 patients used to test the predictive model.

The former is to be expected because age is included in the APACHE II score. However the exclusion of albumin, a highly significant variable in determining the probability of death in our previous study,[3] or of complications in other studies[12] was not anticipated; it would appear that APACHE II measures altered physiologic status better than the low serum albumin. This evidence supports the hypothesis that the low serum albumin in these acutely ill patients measures an 'acute-phase response.' During an acute-phase response, albumin synthesis and release is 'down regulated,' whereas acute-phase proteins such as the C-reactive protein are 'up regulated.'[13] However the limited number of deaths may also explain the failure to identify more than two strong predictor variables.

The clinical usefulness of the predictive equation presented in this article relies on several factors. First the model has been validated on a wide variety of patients, including both acute and elective, intensive care and ward,

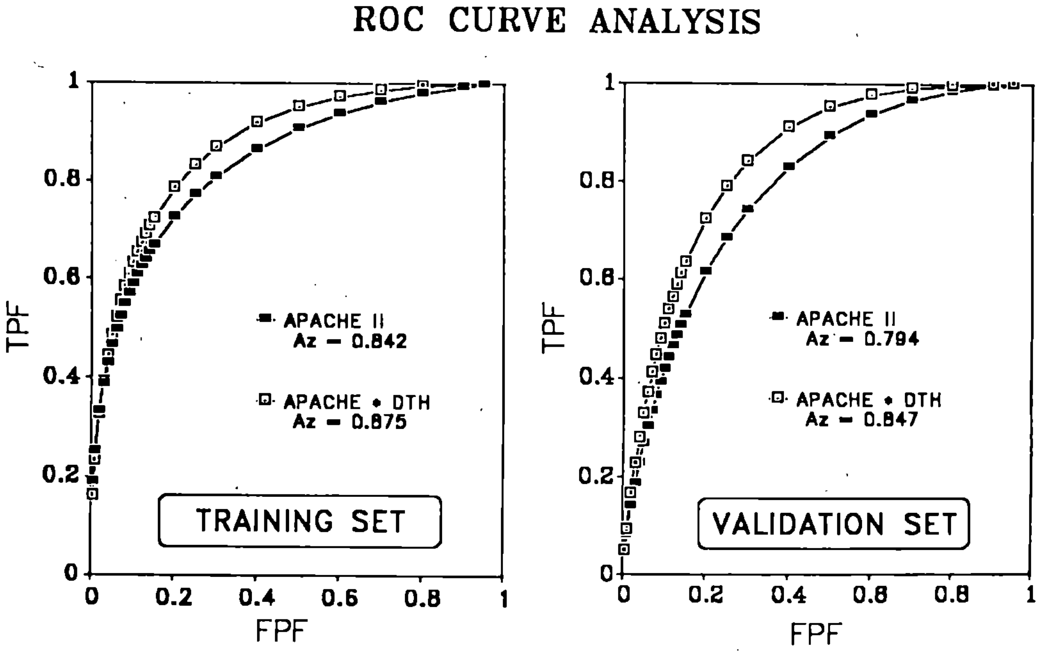

FIG. 5. Receiver operating characteristic curves for the APACHE II equation and the combined APACHE II + DTH score equation in the training set (118 patients) and the validation set (354 patients). TPF, true predictive factor; FPF, false predictive factor; $A_z$, area under ROC curve.

TABLE 6. *Statistical Comparison of Goodness-of-fit of the Two Predictive Models*

| | Training | | Validation | |
|---|---|---|---|---|
| Statistic | APACHE II | DTH + APACHE | APACHE II | DTH + APACHE |
| Chi square | 34.7 | 33.3 | 41.6 | 56.3 |
| Goodman–Kruskal G statistic | −0.78 | −0.83 | 0.68 | 0.77 |
| ROC $A_z$ | 0.842 | 0.875 | 0.794 | 0.847 |

DTH, delayed-type hypersensitivity; ROC, receiver operating characteristic.

[ROC $A_z$ = area under ROC curve].

septic and nonseptic admissions. While the APACHE II score remains the choice stratification system in the ICU setting, the combined estimate can be of use in a much wider surgical population. Second the test provides an accurate estimate of probability of death for each individual patient rather than just a score. Finally the increased 'predictive power' was obtained with the addition of the DTH response. This indicates that host immunocompetence is important in determining outcome of a critically ill surgical patient. Any therapeutic strategy aimed at improving outcome in such patients should account for both physiologic and immunologic alterations of the host. This estimate can be used in clinical decision making as well as in monitoring various therapies aimed at improving a patient's nutritional and immune status.

## References

1. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13:818–822.
2. MacLean LD, Meakins JL, Taguchi K, et al. Host resistance in sepsis and trauma. Ann Surg 1975; 182:207–215.
3. Christou NV. Predicting septic related mortality of the individual patient based on admission host-defence measurements. Can J Surg 1986; 29:424–428.
4. Cox DR. The Analysis of Binary Data. New York: Halsted, 1970.
5. BMDP Statistical Software. Berkeley, University of California Press, 1988.
6. Goodman LA, Kruskal WH. Measure of association for cross classifications. J Am Stat Assoc 1954; 49:732.
7. Hanley JA, McNeil BJ. The meaning and use of the area under a Receiver-Operating-Characteristic (ROC) curve. Radiology 1982; 143:29–33.
8. Metz CE, Wang PL, Kronman HB. A new approach for testing the significance of differences between ROC curves measured from correlated data. *In* Deconick F, ed. Information Processing in Medical Imaging VIII. The Hague: Martinus Nijhof, 1984.
9. Knaus WA, Zimmerman JE, Wagner DP, et al. APACHE—acute physiology and chronic health evaluation: a physiologically based evaluation system. Crit Care Med 1981; 9:591–596.
10. Johnson WC, Ulrich F, Mequid MM, et al. Role of delayed hypersensitivity in predicting postoperative morbidity and mortality. Am J Surg 1979; 137:536–540.
11. Christou NV, Tellado-Rodriguez J, Chartrand L, et al. Estimating mortality risk in preoperative patients using immunologic, nutritional, and acute-phase response variables. Ann Surg 1989; 210:69–77.
12. Mullen JL, Gertner MH, Buzby GP, et al. Implications of malnutrition in the surgical patient. Arch Surg 1979; 114:121–126.
13. Sganga G, Siegel JH, Brown G, et al. Reprioritization of hepatic plasma protein release in trauma and sepsis. Arch Surg 1985; 120:187–191.

# The Role of Calcium Ions and Calcium Channel Entry Blockers in Experimental Ischemia–Reperfusion-induced Liver Injury

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**Verapamil administered before treatment, but not after treatment, had a beneficial effect on a 90-minute warm ischemia–reperfusion rat liver injury model. The possible activation of proteases converting the xanthine dehydrogenase to xanthine oxidase, the significant mitochondrial calcium loading during the ischemic period, and the potentiation of calcium and oxygen-derived free radicals to promote injury to mitochondria are mechanisms supported by this study, based on both histologic observations and on the pattern of enzyme leak after the acute ischemic event.**

LIVER ISCHEMIA MAY occur in patients operated on for trauma,[1] cancer,[2] or hepatic transplantation.[3] Hepatic failure unassociated with surgery, but following a period of hemodynamic or cardiogenic shock, is a well-recognized phenomenon.[4,5]

Although such conditions may result in hypoperfusion of liver cells and eventual hepatocyte dysfunction, the mechanisms by which postischemic liver damage occurs are not clear. In the past two decades, many potentially damaging factors, such as adenosine triphosphate (ATP) depletion, activation of autolytic systems, cellular acidosis, superoxide-induced membrane change, and mitochondrial dysfunction have been implicated as playing roles in ischemic injury.[6] Steroids,[7] dopamine,[8] ATP,[9] alpha tocopherol,[10] activated carbon hemoperfusion,[11] allopurinol,[12-14] superoxide dismutase, and catalase[13-15] have been implicated as theoretically protective agents addressing these factors.

Recent interest has been displayed in the calcium-blocking agent verapamil for protection of hearts subjected to global ischemia, and for protecting against postischemic acute tubular necrosis in acute renal failure models.

Previous work in our laboratory defined a pattern of hepatic enzyme leak that is substantially and predictably elevated over sham-operated controls[13] and showed that this enzyme leak corresponds to a pattern of histologic damage most evident at day 2 and resolved by 3 weeks after operation.[14]

The present experiments were designed to study the role of administered verapamil on the histologic and biochemical response to an *in vitro* timed liver ischemic episode of 90 minutes, and, by inference, the role of ionized calcium and calcium channel blockade in the mediation of ischemia–reperfusion liver injury.

## Material and Methods

Sprague-Dawley rats weighing 280 to 330 g were fasted for 12 hours before experiments but were allowed water *ad libitum*. The animals were anesthetized with ketamine (10 mg/kg body weight) plus innovar (0.1 mL/kg body weight), and the internal jugular vein was exposed for drug administration. Midline laparotomy was performed and 100 units of heparin were administered. The liver hilus was exposed, and the portal vein, hepatic artery, and bile duct of the left lateral and median lobes of the liver were occluded by a small vascular clamp distal to the origin of the vessels supplying the omental (caudate) and right lobe, as previously described. The blood supply to the omental and right lobes was uninterrupted and the portal blood flow was maintained through them without evidence of vascular congestion of the alimentary tract. The abdominal incision was temporarily closed by towel clips, and the animals were maintained anesthetized in the Research Resources Facility of Georgetown University. Reperfusion was induced by declamping the vessels after 90 minutes of ischemia, the abdomen was closed in two layers with 3-0 silk sutures, and the animals were allowed to recover.

Three groups of 20 rats each were used in this study. All rats had blood determinations of lactic dehydrogenase (LDH), serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, sorbitol dehydrogenase, alkaline phosphatase, and total and direct bilirubin before operation and at 2, 7, 14, and 21 days after ischemia. Rats were killed on day 21. Liver biopsies were performed at

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the time of initial laparotomy before the induction of ischemia, 2 days after operation, at 1 and 2 weeks, and at the time the animals were killed. All of the biopsies were performed by laparotomy under a ketamine-innovar general anesthesia.

Light microscopic review was performed by the pathologist in a blinded fashion and fatty deposition and centrilobular necrosis were rated as absent, moderate, or severe.

The drug treatment regimens (excluding the heparin, ketamine, and innovar, which all animals received) were as follows: group A, none (control group); group B, verapamil before treatment (0.3 mg/kg body weight intravenously as a bolus *via* the internal jugular vein before the induction of the liver ischemia); and group C, verapamil after treatment (0.3 mg/kg body weight intravenously as a bolus *via* the internal jugular vein beginning 1 minute before the liver hilus declamping and continuing intravenous administration for 2 minutes during early reperfusion).

Results of the enzyme determinants are expressed as the mean of these values plus or minus the standard de-

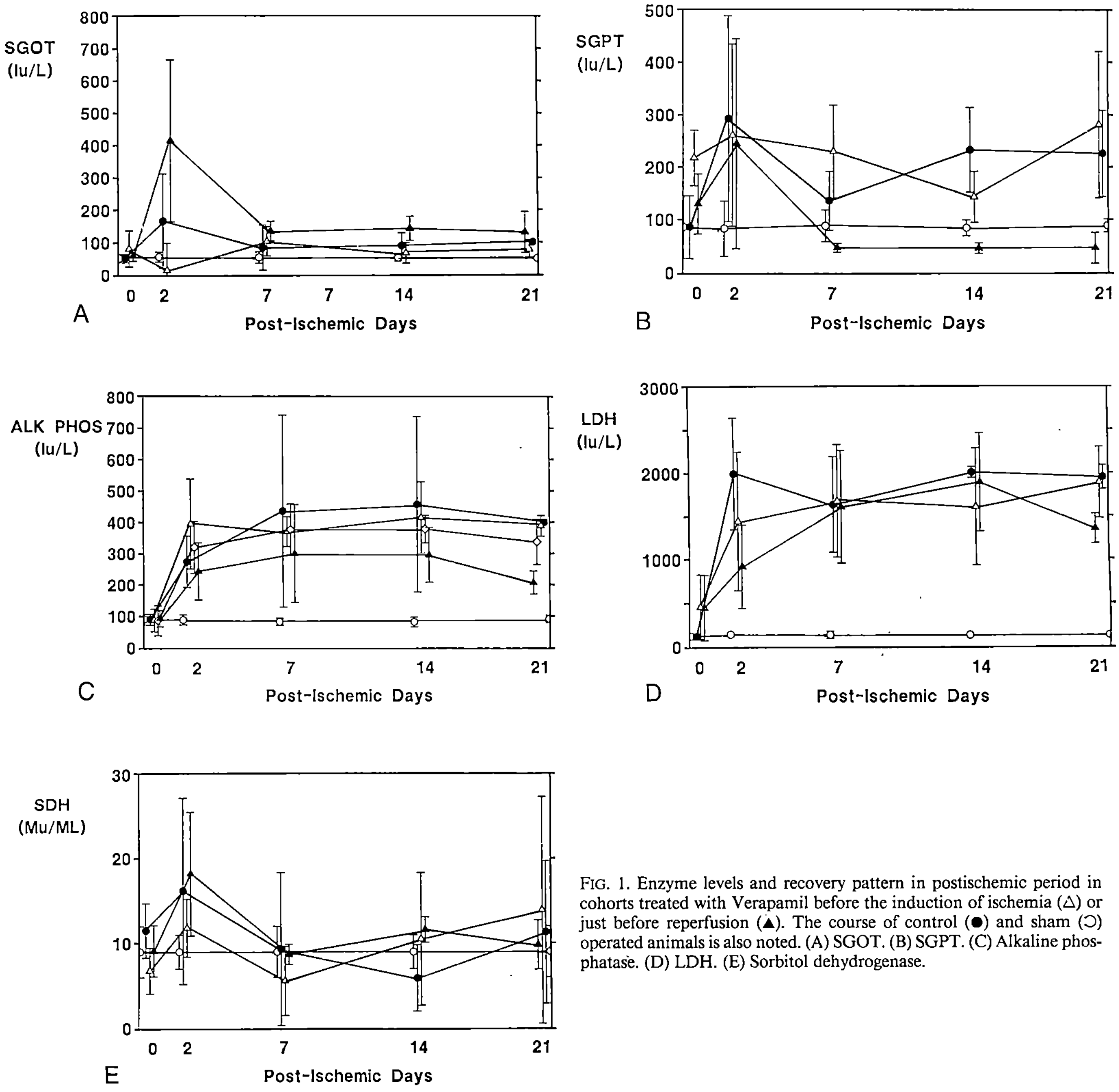


FIG. 1. Enzyme levels and recovery pattern in postischemic period in cohorts treated with Verapamil before the induction of ischemia (△) or just before reperfusion (▲). The course of control (●) and sham (○) operated animals is also noted. (A) SGOT. (B) SGPT. (C) Alkaline phosphatase. (D) LDH. (E) Sorbitol dehydrogenase.

viation. Student's t test and chi square test were used to analyze differences.

### Results

During the ischemic period, portal flow was satisfactory through the uninterrupted circulation of the nonischemia liver lobes without evidence of vascular congestion of the alimentary tract.

The mean and the standard deviation of all biochemical assays in each group is presented in Figure 1.

Serum glutamic oxaloacetic transaminase values in group A (control) showed a significant change on days 2, 14, and 21. This was also true in the verapamil post-treatment group, whereas in group B, no significant increase was noted. On the second day, group C had significantly higher levels than the control group ($p < 0.005$) and group B ($p < 0.005$). On the 14th day, group C maintained significantly higher levels than group A ($p < 0.001$). By 21 days after ischemia, no significant differences were observed. Serum glutamic pyruvic transaminase values were increased significantly during the entire postischemic period in the control group. However, in group C, a significantly elevated level was only measured on postoperative day 2 ($p < 0.02$), and no significantly higher ($p < 0.001$ every day) levels in group A were noted each day when compared to group C.

In groups A and C, significantly increased levels of alkaline phosphastase during the entire postischemic period were observed. No significant increase in group B was noted. In group C significantly higher levels were noted than in the control group at days 2 and 21 ($p < 0.001$).

In all groups significantly increased levels of LDH compared to the preischemic baseline were noted. In the control group, higher levels than in group B were noted only on day 14 ($p < 0.005$). In the control group, values were higher than group C only on days 2 ($p < 0.002$) and 21 ($p < 0.001$).

In group A no significant increased levels of sorbitol dehydrogenase were measured. In group B significant increases on days 2 and 21 were observed, whereas in group C significantly increased levels on days 2 and 14 were noted. In group C a significantly higher level than in group A ($p < 0.001$) was observed on day 14.

No significant total and direct bilirubin level differences in either group were noted when compared to baseline levels. When compared, all groups had identical bilirubin levels throughout the experiment period.

The total number of significantly elevated levels of all the biochemical assays during the postischemia–reperfusion period compared to the preischemic baseline levels were tabulated (Table 1). In group B a significantly better result than in group A or in group C was noted ($p < 0.05$).

### Histologic Findings

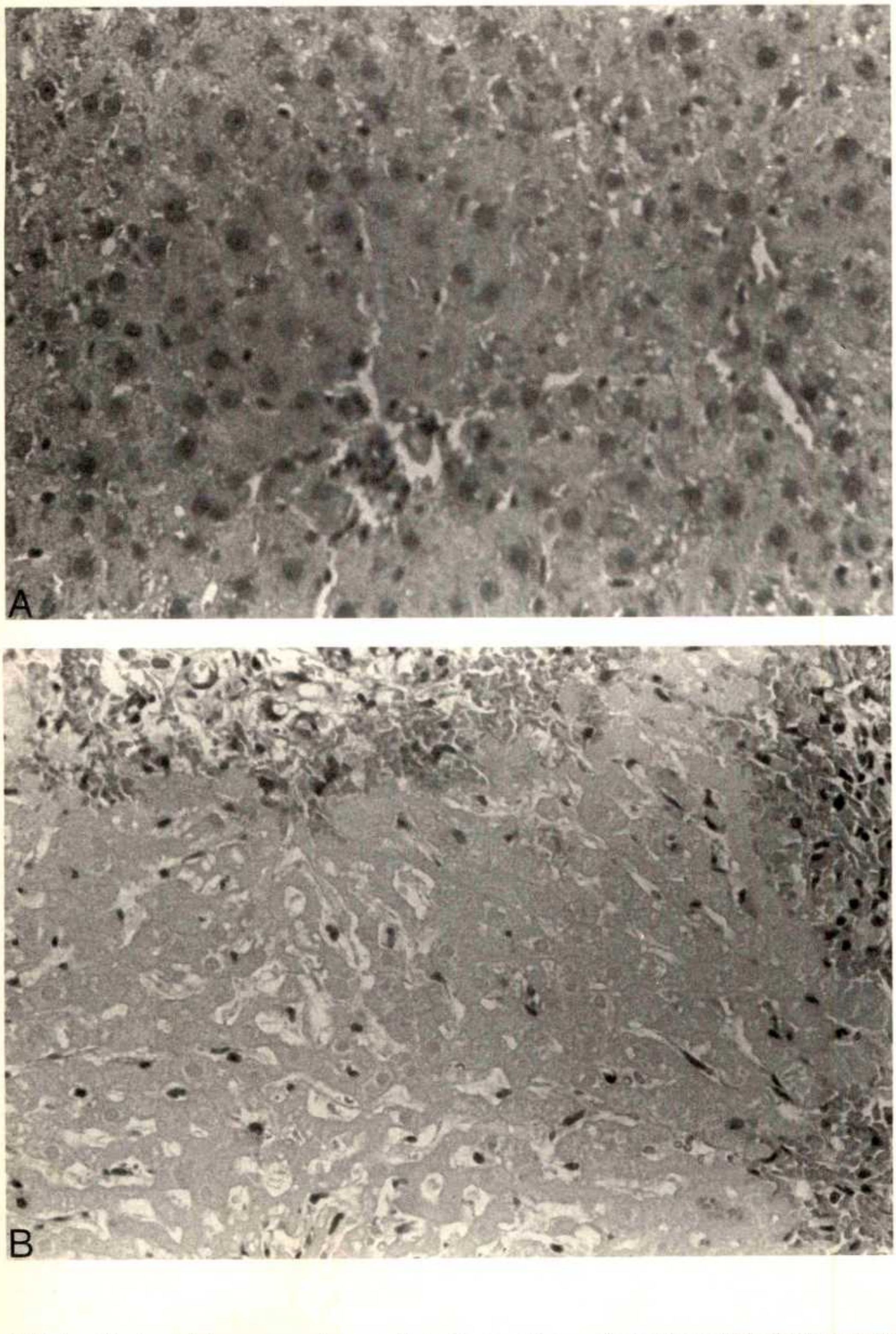
Severe centrilobular liver cell necrosis in groups A and C was observed. In group B the pretreatment use of verapamil had significant protective effect on the ischemia–reperfusion-induced liver injury (Table 1, Fig. 2).

### Discussion

Wait et al.[17] described a chronic clamp-induced model of ischemic renal failure, occluding the renal artery of rats for 45 minutes and then performing contralateral nephrectomy. Fifteen-minute infusions of verapamil to 66 mg/kg were noted to offer protection in this model. Previously we demonstrated[13,14] that 90-minute infusion produces a reproducible histologic injury and biochemical leak pattern and we sought, in these experiments, to test whether the same dose of verapamil would be protective against hepatic ischemia–reperfusion injury. Our results show that verapamil, a slow calcium channel entry blocker, administered before an ischemic insult, had a beneficial effect during the 90-minute period of warm liver ischemia in the *in vivo* rat liver followed through the 21-day reperfusion period. When verapamil was given during the end of ischemia and the early reperfusion period, the biochemical and histologic findings were very close to controls, and minimal, if any, protection was afforded.

TABLE 1.

| Experimental Group | Extent of Centilobular Necrosis | | | | |
|---|---|---|---|---|---|
| | Days Following Ischemic Event | | | | |
| | 0 | 2 | 7 | 14 | 21 |
| Sham | 20 Absent | 20 Absent | 20 Absent | 20 Absent | 20 Absent |
| Group A | 20 Absent | 12 Severe<br>8 Moderate | 12 Severe<br>8 Moderate | 17 Moderate<br>3 Absent | 3 Moderate<br>17 Absent |
| Group B | | 8 Moderate<br>12 Absent | 4 Moderate<br>16 Absent | 3 Moderate<br>17 Absent | 2 Moderate<br>18 Absent |
| Group C | | 13 Severe<br>7 Moderate | 13 Severe<br>7 Moderate | 16 Moderate<br>4 Absent | 5 Moderate<br>10 Absent |



FIGS. 2A and B. (A) Moderate centrilobular necrosis. Note some preservation of portal architecture. (B) Severe centrilobular necrosis.

This implicates calcium as a primary etiologic agent in ischemic cell injury.

In heart models others have found similarly that to be protective, the drug must be given before the induction of global ischemia.[16] It is believed in this model that calcium channel blockers protect the heart from oxygen and substrate deprivation by decreasing the contractile activity and the energy demand.[19] Although the time of drug administration with respect to the insult appeared less critical in kidney models, verapamil has been reported to protect kidneys from the acute ischemic renal failure induced by norepinephrine,[20] cold,[21] or warm ischemia.[17,21] In other studies it was demonstrated that verapamil had global beneficial effects when given to dogs during a 2-hour period of hemorrhagic shock.[22] The drug partially or completely prevented the development of ventricular subendocardial necrosis and hemorrhage and of zonal lesions resulting in less intestinal mucosal hemorrhage and effecting a significantly higher survival rate.

In ischemic states elevated levels of calcium in cells or tissues have been observed in *in vitro* models. In rat kidneys that were rendered ischemic for 45 minutes, mitochondria isolated before reperfusion had marked impairment of respiratory function but only slightly increased levels of calcium.[25] During reflow the mitochondrial calcium increased progressively so that a mitochondrial calcium loading occurred despite improvement in respiratory function within 1 to 4 hours of reperfusion.[20,25] Verapamil has been shown to prevent this mitochondrial calcium loading and mitochondrial respiratory dysfunction.[20] In contrast to these studies of warm ischemia and cold ischemia, a significant calcium loading occurs during the ischemic period, and the protective effects of verapamil appear to take place during the ischemia and not during reflow.[21]

In liver ischemia, no direct evidence of the role of slow calcium channel entry blockers has been reported in a chronic model.

Verapamil was protective, if present, during the ischemic period, but not if administered after established ischemia. This suggests that high levels of calcium in cells or tissues might contribute to the deleterious events leading to cellular injury.[19]

Different mechanisms could explain this phenomenon, none of them giving clear evidence of calcium's role in cellular injury. In fact all inferences to date with respect to the role of calcium in liver injury have been indirect. The salutary effect of chlorpromazine,[23] thought to be protective by inhibiting calcium-dependent processes by binding to calmodulin,[24] is an example of such an inference.

One proposed mechanism of the protection afforded by verapamil relates to the conversion of xanthine dehydrogenase to xanthine oxidase, which is the main source of the superoxide radical.[26] The elevated cytosolic calcium concentration during ischemia, it is believed, activates a protease capable of converting the dehydrogenase to the oxidase. The xanthine oxidase can use molecular oxygen during reperfusion, producing superoxide anion and, secondarily, hydrogen peroxide and hydroxyl radical. These oxygen-derived free radicals are responsible for ischemia-reperfusion-induced liver injury.[13,14] The present study is unable to contradict this theory.

The second proposed mechanism, one that relates to cellular calcium loading during reperfusion,[20,25] is not supported by this study because no protective effect of verapamil was noted when the drug was given during the reperfusion period.

The second proposed mechanism, one that relates to cellular calcium loading during the period of cold ischemia, could be supported by our study if it is known that calcium loading during warm ischemia also is present.

Recent evidence[27] indicates that calcium potentiates the damaging effect of oxygen-derived free radicals on the mitochondrial electron transport chain due to impairment of NADH-coenzyme Q-reductase activity. This interesting fourth proposed mechanism is supported by this study.

## Acknowledgment

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## References

1. Numes G, Blaisdell F, Margaretten N. Mechanism of hepatic dysfunction following shock and trauma. Arch Surg 1970, 100:546–556.
2. Starzl T, Bell R, Beart R, Putnam R. Hepatic trisegementectomy and other liver resections. Surg Gynecol Obstet 1975, 141:429–437.
3. Toledo-Pereyra L. Improvement of liver transplant survival: new avenues of research. Transplant Proc 1985, 17:298–301.
4. Champion R, Jones R, Trump B, et al. A clinicopathologic study of hepatic dysfunction following shock. Surg Gynecol Obstet 1976, 142:657–663.
5. Bulkley G, Oshima A, Bailey R. Pathophysiology of hepaic ischemia in cardiogenic shock. Am J Surg 1986, 151:87–97.
6. Leaf A, Cheung J, Mills J, Bonventre J. Nature of the cellular insult in acute renal failure. *In* Brenner B, Lazarus J, eds. Acute Renal Failure. Philadelphia: WB Saunders, 1983; pp 2–20.
7. Fornander J, Hellman A, Hasselgren P. Effects of methylprednisone on protein synthesis and blood flow in the post-ischemic liver. Circ Shock 1984, 12:287–295.
8. Hasselgren P, Biber B, Fornander J. Improved blood flow and protein synthesis in the post-ischemic liver following infusion of dopamine. J Surg Res 1983, 34:44–52.
9. Clemens M, McDonagh P, Chaudry I, Bave A. Hepatic microcirculatory failure after ischemia and reperfusion: improvement with ATP-$MgCL_2$ treatment. Am J Physiol 1985, 248:H804–H811.
10. Marubayashi S, Dohi K, Ochi K, Kawasaki T. Role of free radicals in ischemic rat liver cell injury: prevention of damage by a-tocopherol administration. Surgery 1986, 99:184–191.
11. Toledo-Pereyra L. Role of activated carbon hemoperfusion in the recovery of livers exposed to ischemic damage. Arch Surg 1985, 120:462–465.
12. Nordstrom G, Seeman T, Hasselgren P. Beneficial effect of allopurinol in liver ischemia. Surgery 1985, 97:679–683.
13. Nauta R, Uribe M, Walsh D, et al. Histopathologic correlates of murine hepatic ischemic reperfusion injury: evidence from a chronic in vivo model. J Inv Surg 1988, 1:155–162.
14. Nauta R, Uribe M, Tsimoyiannis E, et al. Description of a chronic in-vivo murine model for the study of warm hepatic ischemia/reperfusion injury. Surg Res Comm 1989 (In press).

15. Granger D, Adkinson D, Hollwarth M, et al. Role of oxygen free radicals in ischemia-reperfusion injury to the liver. Gastroenterology 1985, 88:1662(Abstr).
16. Watts J, Koch C, Lanoue K. Effects of $Ca^{2+}$ antagonism on energy metabolism: $Ca^{2+}$ and heart function after ischemia. Am J Physiol 1980; 232:H909–H916.
17. Wait R, White G, Davis T. Beneficial effects of verapamil on post-ischemic renal failure. Surgery 1983, 94:276–282.
18. Baker H de C. Ischemic necrosis in the rat liver. J Pathol Bact 1956, 71:135–143.
19. Cheung T, Bonventre J, Malis C, Leaf A. Calcium and ischemic injury. N Eng J Med 1986, 314:1670–1676.
20. Burke T, Arnold P, Gordon J, et al. Protective effect of intrarenal calcium membrane blockers before or after renal ischemia: functional, morphological, and mitrochondrial studies. J Clin Invest 1984, 74:1830–1841.
21. Shapiro J, Cheung C, Itabashi A, et al. The effect of verapamil on renal function after warm and cold ischemia in the isolated perfused rat kidney. Transplantation 1985, 40:596–600.
22. Hackel D, Mikat E, Whalen G, et al. Treatment of hemorrhagic shock in dogs with verapamil: effects on survival and on cardiovascular lesions. Lab Invest 1979, 41:356–359.
23. Mittnacht S, Farbet J. Reversal of ischemic mitochondrial dysfunction. J Biol Chem 1981, 256:3199–3206.
24. Godfraind T. Calcium entry and calcium entry blockade. *In* Godfraind T, et al., eds. Calcium Entry Blockers and Tissue Protection. New York: Raven Press, 1985; pp 1–19.
25. Wilson D, Arnold P, Burke T, Schrier R. Sequential changes in mitochondrial function in ischemic acute renal failure in the rat. Kidney Int 1983, 23:209(Abstr).
26. McCord J. Oxygen-derived free radicals in post-ischemic tissue injury. N Eng J Med 1985, 312:159–163.
27. Malis C, Bonventre J. Mechanism of Ca and oxygen free radical injury to the mitochondrial electron transport chain. Kidney Inst 1986, 29:305(Abstr).

# Organ Procurement in Patients with Fatal Head Injuries

## *The Fate of the Potential Donor*

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**A 46-month, retrospective review of all victims of fatal head injury at a level 1 trauma center was undertaken to estimate donor organ availability, determine causes of procurement failure, and analyze the functional results of organs transplanted from this group of donors. Causes of procurement failure in 126 patients who died principally from their head injuries included failure of initial resuscitation (14%), ineligibility (28%), failure of physiologic support (14%), and denial of consent (20%). Of 73 eligible donors, 29 (41%) were able to donate one or more vascular organs (heart, liver, kidney). In only one instance was an eligible donor not appropriately identified as such. Failure of physiologic support to prevent early death (25%), and denial of consent (34%) were found to be the two major, potentially remediable causes of procurement failure in this series. Based on this data, an estimated 29 patients/million population/year will survive initially and meet all eligibility requirements for organ donation. Data on 47 kidneys transplanted from the donor group demonstrated a 77% overall graft survival rate at a follow-up period averaging 23 months. Prolonged donor hypotension, but not the use of high-dose vasopressors, adversely affected allograft survival. The current limitations of organ procurement in victims of fatal head injury stem from a limited ability to maintain cardiopulmonary function long enough for the procurement process to be completed and a high overall rate (46%) of denial of consent for organ harvest by next of kin.**

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ORGAN TRANSPLANTATION HAS become an increasingly effective means of treating end-stage cardiac, renal, and hepatic disease. The proliferation of organ transplantation programs coupled with technical and immunologic improvement in recipient management produced an expansion in the number of potential recipients and increases in the demand for donor organs. Further expansion of organ transplantation may be limited by the availability of viable donor organs.[1,2] Previous studies examining organ availability reported distressingly low organ procurement rates from potential donors.[3,4] Many organ procurement failures have been attributed to a failure to identify patients with nonsurvivable central nervous system (CNS) injury or disease as potential organ donors or failure to request consent for donation from next of kin. These causes of procurement failure should be remediable, and laws requiring that request be made of next of kin for organ donation ('required request') have already been passed in an attempt to improve procurement efficacy.[5]

Head injury continues to be the largest cause of brain death and generates the largest number of potential organ donors in many transplant centers.[3,6,7] Trauma systems and centers ideally should act to increase early survival of patients with ultimately fatal head injuries and facilitate the referral of potential donors to an organ procurement agency (OPA), thereby improving organ procurement. Improvements in organ procurement efficacy, beyond 'required request' laws, therefore will depend on a careful evaluation of the procurement process within such a system.

The purpose of this study was to determine the overall efficacy of organ procurement at a level 1 trauma center. The specific aims of the study were to (1) provide a realistic estimate of the availability of donor organs resulting from head injury in a regionalized system; (2) identify the specific reasons for organ procurement failure within such as system; (3) define the type and frequency of specific management problems that occur in potential donors; (4) evaluate the functional outcome of organs transplanted from victims of fatal head injury; and (5) identify any physiologic factors among donors that may affect function of transplanted organs.

### Patients and Methods

The University of California San Diego Medical Center is one of five adult trauma centers in San Diego County. The population for the San Diego County Trauma System is estimated at 2.4 million, including tourists and transients. The University Hospital (UCSD) admits an average of 27% of the adult trauma patients treated annually in the system. From August 1984 through May 1988, all patients with severe head injuries who died after arrival to the hospital were reviewed. Medical records, postmor-

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tem examinations, trauma registry reports, and organ procurement agency records (for potential donors) were reviewed.

All patients included in the study were admitted to the Trauma Service with neurosurgical consultation obtained at the time of admission. Patients identified as having nonsurvivable neurologic injuries were maintained with full cardiopulmonary support until (1) the patient was judged to be (or became) ineligible for organ donation and the next of kin could be notified; (2) next of kin was located and consent for organ donation was denied or a request for withdrawal of support was made; and (3) eligible organs were harvested.

By standing protocol the OPA representative (transplant coordinator) was contacted for any patient judged to have nonsurvivable CNS injuries. Request for organ donation was made for eligible patients, primarily by OPA coordinators, but sometimes by trauma attending physicians or trauma house officers. The determination of brain death followed guidelines similar to those suggested by the President's Commission Report[8] and included a detailed clinical examination, evidence of irreversible structural derangement (based on examination or computed tomography), and an apnea trial.[9] In patients given barbiturates in whom the neurologic examination was not meaningful, additional studies (four-vessel cerebral angiography or radionucleotide imaging) were used to confirm brain death based on the absence of intracranial blood flow.

Demographic data, injury severity scores, prognosis at admission, donor eligibility status, brain death status, response to consent request, cause of death, and organ donation status were tabulated for each patient. Physiologic data, including systolic blood pressure, arterial blood gases, duration of hypotension (blood pressure less than 90 mmHg), urine output, and serum electrolytes, were also recorded. The presence or absence of each of five conditions were recorded for each patient: (1) hypotension, defined as a sustained (more than 5 minutes) systolic blood pressure less than 90 mmHg; (2) pulmonary edema (neurogenic), based on chest x-ray, observed airway edema/froth, postmortem examination, and the absence of other factors promoting lung edema; (3) hypothermia, defined as a minimum recorded temperature of 92 F or less; (4) massive diuresis, often multifactoral in etiology, defined on the basis of electrolyte profiles (diabetes insipidus) or a urine output in excess of 800 mL/hr with associated volume depletion; (5) coagulopathy, defined using coagulation studies (more than twice control) or observed abnormal clinical bleeding.

Follow-up data on 47 of 48 renal transplant recipients was obtained with an average follow-up interval of 23 months. Early and late graft function was correlated to the presence of prolonged hypotension (systolic blood pressure less than 90 mmHg for more than 1 hour), or to the use of high-dose vasopressors (dopamine more than 10 $\mu$g/kg/min) in the organ donor.

Data was assembled using a computerized database (DB3 plus) and analyzed using a standard statistical package (Medically Related Time Oriented Database, Retriever Systems, Inc.). Categorical data were assessed using Fisher's Exact Text, or chi squared analysis, without Yate's correction for continuity. Significance was attributed at $p < 0.05$.

## Results

During the 46-month review period, 190 patients died after major head injury. Of this group, 50 patients were excluded from analysis who sustained severe head injuries but in whom death could not be attributed solely to intracranial injury. The cause of death in an additional 14 head injury patients was judged to be principally from non-CNS causes. The remaining 126 patients sustained either isolated head injury or severe head injuries with associated injuries that did not contribute to their death. This study group represents the 'cleanest' group of potential organ donors that could be identified.

Most of these patients (90 of 126, [71%]) were identified as having nonsurvivable injuries at the time of admission. The average Glasgow Coma Score for all patients was 4.2. Multiple causes of procurement failure were identified (Fig. 1). Patients who could not be resuscitated on arrival to the hospital trauma unit or operating room (n = 18) died of refractory hypotensive cardiac arrest. Their average survival time after hospital arrival was 31 minutes. The average time from injury to death in these patients was approximately 2 hours and included delays for transfers from Mexico and out-of-county locations.

Of the 108 initial survivors, 35 were not eligible to donate organs (principally kidneys) (Fig. 1). Renal failure as a cause of ineligibility occurred early in the hospital course (less than 3 days) and was unrelated to the severity or duration of hypotension. Pneumonia was the principal source of infection in patients with sepsis. Four patients continued to have spontaneous ventilatory activity and became ineligible because of lack of evidence of clinical brain death. These patients were all hemodynamically stable and could have been maintained for some period of time. In most cases the families requested withdrawal of support, and it was deemed inappropriate to provide prolonged physiologic support solely for purposes of organ procurement.

Of 73 eligible patients, 29 (40%) were able to donate one or more vascular organs. Despite protocols for OPA contact, one potentially eligible donor had support withdrawn inappropriately, without consideration given to the possibility of organ donation. The two principal causes

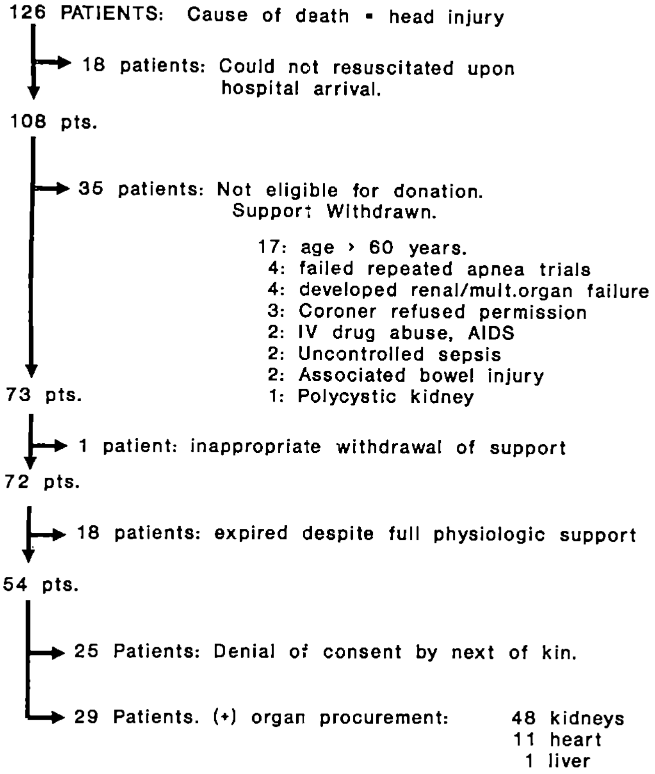
126 PATIENTS: Cause of death • head injury
18 patients: Could not resuscitated upon hospital arrival.
108 pts.
35 patients: Not eligible for donation. Support Withdrawn.
17: age › 60 years.
4: failed repeated apnea trials
4: developed renal/mult.organ failure
3: Coroner refused permission
2: IV drug abuse, AIDS
2: Uncontrolled sepsis
2: Associated bowel injury
1: Polycystic kidney
73 pts.
1 patient: inappropriate withdrawal of support
72 pts.
18 patients: expired despite full physiologic support
54 pts.
25 Patients: Denial of consent by next of kin.
29 Patients. (+) organ procurement:
48 kidneys
11 heart
1 liver

FIG. 1. Causes of organ procurement failure among 126 potential donors.

of procurement failure in eligible victims were failure of physiologic support measures (18 of 73 patients [25%]) and denial of consent (25 of 73 patients [34%]) (Fig. 1).

One of the contributing factors in the 18 potential donors who died before completion of the organ procurement process were the short survival times (Fig. 2). The mean survival time for all patients was 64 hours. Survival in patients who died despite full physiologic support was extremely short with approximately a 60% mortality rate at 12 hours. Delays in the organ procurement process at various steps contributed to the loss of organs in this group of potential donors (Table 1). Delays in brain death determination resulted from hypotension, hypothermia, or drugs in four patients. Delays in the formal documentation of brain death occurred in seven patients. Delays in locating next of kin resulted in the loss of three potential donors.

The major causes of death in the 18 patients who were fully resuscitated on arrival but who subsequently died despite full cardiopulmonary support were refractory hypotension (n = 12), bradycardia and arrest (n = 4), and overwhelming pulmonary edema (n = 2). Physiologic problems encountered in the management of fatal head injuries included hypotension, coagulopathy, neurogenic pulmonary edema, hypothermia, and massive diuresis (as previously defined). Each occurred frequently and often in combination (Table 2).

The overall consent rate was 54% and was lower in some ethnic groups (Table 3). Analysis of frequency of consent *versus* denial by racial origin shows a significantly skewed distribution (p = 0.003), with white victims supplying the vast majority of donated solid organs.

Follow-up data on 47 transplanted kidneys were available for 24 donors (Table 4). There were not enough fol-

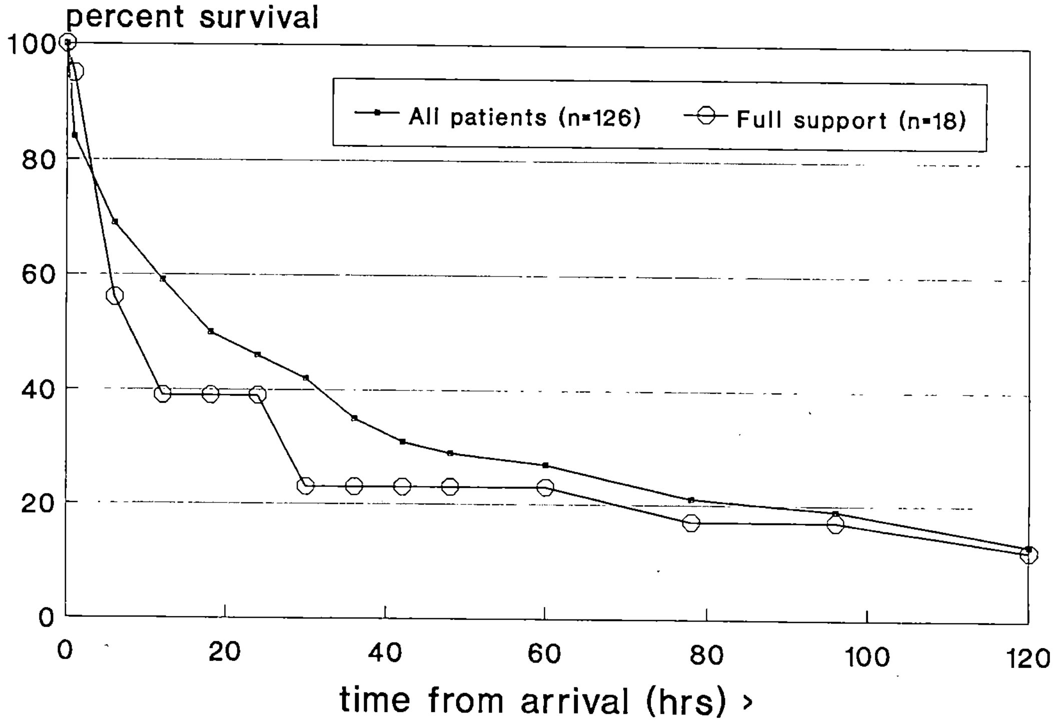

FIG. 2. Patient survival rate as a function of time. Solid squares = all potential organ donors. Open circles = 18 patients, initially resuscitated, who subsequently died despite full physiologic support.

TABLE 1. *Circumstances Associated with Failure of Extended Physiologic Support in 36 Patients with Lethal Head Injuries*

| Number of Patients | Circumstance(s) |
|---|---|
| 18 | Could not be resuscitated on arrival |
| 4 | Declared brain dead<br>3 died awaiting search for next of kin<br>1 died awaiting harvest (4 hrs. after declaration, 2.5 hrs. following consent) |
| 4 | Delay in eligibility for brain death determination<br>2: hypothermia<br>1: drugs on board<br>1: persistent hypotension |
| 3 | Unexpected late death from sudden herniation/ arrhythmias |
| 7 | Delay in documentation of brain death<br>All nonsurvivable on admission; no apnea trials were performed; average survival, 7.1 hours. |

low-up data available on the 11 heart recipients to allow meaningful analysis. Physiologic data from the donors demonstrated that a systolic blood pressure of less than 90 mmHg sustained for a period exceeding 1 hour was associated with an increased late renal graft failure rate (Table 4). There was no significant association between early or late graft failure rates and the preharvest use of pressors for support of blood pressure, massive diuresis, or hypothermia.

Based on an average estimated catchment population of 2.4 million for the entire San Diego trauma system, and assuming comparable rates of fatal head injury for other areas in the system, the organ recovery rate for adults is estimated at 12 actual donors/million population/year. The number of eligible donors surviving to hospital admission is estimated at 29/million population/year.

## Discussion

The increasing success of transplantation as a means of treating end-stage disease has focused attention on the need for improvement in the organ procurement process. At the end of 1988, formal waiting lists for organ transplants included more than 14,850 potential renal transplant recipients, 1269 potential cardiac transplant recipients, and more than 800 potential liver transplant recipients.[10] The actual number of potential recipients may be substantially higher. In addition the continuing efforts to reduce mortality and morbidity rates associated with CNS disease and injury ultimately will act to reduce the total supply of donor organs and place further emphasis on increasing the efficiency of the procurement process for those victims of incurable disease or fatal injury.

Reductions in morbidity and mortality from other injuries has made head injury the principal cause of death in a modern level 1 trauma system.[11] In several reports, organs procured from trauma victims constituted between 55% and 77% of total donors,[1,7] making trauma the principal source of cadaveric organs for transplantation as well.

The degree to which the increasing demand for transplantable organs can be met by currently available sources is unclear. Previous reports have estimated the total annual need for donors in the United States to be between 10,000 and 15,000.[1,2] With regard to organ availability, Bart[6] estimated the potential availability of donors from all causes at 55 donors/million population/year and concluded that the need for donor organs may be met substantially by the estimated supply. Similarly Oksa,[12] in another autopsy study, estimated this optimal availability to be 45 donors/million population/year. Neither of these studies examined trauma victims separately, and, because of the retrospective nature of the definition of 'potential,' both probably overestimated actual donor organ availability.

The estimate of 12 actual donors/million population/ year calculated from this data falls well short of the anticipated demand. With improvements in the organ procurement process, however, this number could be increased to as much as 29 donors/million population/year, representing roughly 40% to 60% of the predicted need from trauma alone. The underlying assumption, however, that similar injury and procurement rates could be applied to the rest of the country may not be justified entirely, and the actual number of potential donors possibly is less.

### *Causes of Procurement Failure*

Previous work examining organ procurement rates from both trauma and nontrauma victims have demonstrated the generally poor efficacy of the procurement process. In a collaborative review of CNS deaths in Georgia, a Center for Disease Control study in 1983 Bart et

TABLE 2. *Medical Problems Encountered in the Resuscitation and Treatment of Lethal Head-injured Patients*

| Problem | Frequency | Percentage | Treatment Required |
|---|---|---|---|
| Hypotension | 59/91 | 65 | Volume replacement (all) vasopressors |
| Hypothermia | 40/98 | 41 | Active external warming |
| Pulmonary edema | 56/108 | 52 | PEEP, incr. FiO2 |
| Coagulopathy | 39/92 | 42 | Platelets and/or FFP |
| Massive diuresis/diabetes insipidus | 38/99 | 38 | Volume replacement AVP, DDAVP administration |

AVP, arginine vasopressin; FFP, fresh frozen plasma; DDAVP, desmopressin acetate.

TABLE 3. *Consent Rates for Vascular Organ Donation by Ethnic Origin (n = 126)*

| Ethnic Origin | Percentage of Total (n = 126) | Requests Made: Eligible Donors (n = 54) | Consent Given/Denied (% consenting) |
|---|---|---|---|
| White | 56 | 25 (46%) | 19/6 (76) |
| Hispanic | 25 | 16 (30%) | 7/9 (44) |
| Black | 7 | 6 (11%) | 0/6 (0) |
| Asian | 5 | 2 (4%) | 1/1 (50) |
| Other | 7 | 5 (9%) | 2/3 (40) |

al.[4] found the overall organ procurement rate from potential donors to be only 16%. Similarly Morris[13] reported a potential donor/actual donor rate of 23%. The actual function of the organ procurement process (Table 5) is far from optimal in many instances. In addition to patients who were not eligible, loss of potential donors can be attributed to three major problems with the organ procurement process: (1) failure to properly identify potential donors, refer to an organ procurement agency, and/or make a request for organ donation; (2) failure of physiologic support measures; and (3) denial of consent.

Problems with the identification of potential donors and OPA referral are longstanding.[14] Attitudes toward organ donation among professionals clearly affect the procurement process.[15] In addition the management of nonsurvivable head injury can be stressful to everyone involved, and nothing can overcome the profound sense of loss and waste associated with the traumatic death of a young, previously healthy individual. Feelings of helplessness and frustration associated with such cases, coupled with ignorance regarding the potential benefits frequently result in ethical responsibilities to both the decedent's wishes (autonomy) and to the potential recipients of transplantable organs (beneficence) being ignored.

Laws requiring that a formal request for organ donation be made in legally brain dead patients are now in effect in many states. These 'required request' laws have been passed in an attempt to reduce the number of potential organs needlessly wasted because of failure to identify and refer potential organ donors. Although these laws would appear to have an effect on the number of OPA referrals made and may act to increase the supply of bone and tissue available, their efficacy with respect to vascular organ donation is less clear.[5,16] Many of these statutes, including those in California, mandate that hospitals establish procedures whereby appropriate requests for organ donation are made of the next of kin but make no requirement for documentation or provision for actual enforcement. The ultimate success of the procurement process depends on the commitment of those directly involvement with the management of these patients. Statutes and policies, while acting as a reminder, are not likely to serve as an adequate substitute.

The 40% overall procurement rate (eligible/actual donors) reported in this study is substantially higher than that generally reported and similar to that reported by Morris[13] in a study also conducted at a level 1 trauma center. Problems with missed identification, OPA referral, or inappropriate withdrawal of support, with a single exception, did not exist in this study. The two principal, and potentially correctable, problems identified in this study were failure of life support measures and denial of consent.

The data demonstrate that patients with fatal head injury have an extremely short average survival time, even when fully supported (Fig. 2). Previous reports have demonstrated a similar high early mortality rate, with approximately 50% of potential donors dying within 24 hours.[17]. Organ procurement under these circumstances is not a leisurely or 'elective' process and is not something that is undertaken as an afterthought when therapeutic efforts fail and/or patients become moribund. The services and facilities required by the organ procurement process ideally should be available on short notice 24 hours a day (Table 5), and identification of potential donors should be made as early as possible. The contention that potential organ donors may be difficult to identify is not supported by our observation that 55 of 73 patients (75%) were identified at the time of admission as having nonsurvivable injuries.

Delays in the procurement process, many unavoidable, were associated with most of the failures of physiologic support (Table 1). Despite aggressive management directed at preserving cardiopulmonary and renal function, 18 patients with nonsurvivable injuries died before the procurement process could be completed. Most delays in the procurement process that occurred involved delays in eligibility for, or declaration of, brain death.

The condition of brain death, legally defined in most states, requires that there be irreversible cessation of all brain function.[18] Irreversibility usually is documented by

TABLE 4. *Follow-up Renal Transplant Results: 24 Donors, 47 Kidneys*

| Renal Allograft Outcome | Totals | BP > 90 mmHg | BP < 90 mmHg | Pressors | No Pressors |
|---|---|---|---|---|---|
| Immediate graft function without dialysis | 32/47 (68%) | 19/25 (76%) | 13/22 (59%) | 24/36 (67%) | 8/11 (73%) |
| Function at hosp. discharge without dialysis | 36/47 (76%) | 19/25 (76%) | 16/21 (76%) | 28/35 (80%) | 7/11 (64%) |
| Good function at follow-up, without dialysis | 36/47 (77%) | 22/25 (88%)* | 14/22 (64%) | 27/35 (77%) | 9/11 (81%) |

* $p < 0.05$ compared to BP < 90 mmHg.

BP, blood pressure

TABLE 5. *The Organ Procurement Process*

| Function | Service/Facility |
|---|---|
| Rapid transport to definitive care | 911 or equivalent emergency medical system, |
| Appropriate resuscitation | Trauma center or equivalent |
| I.D. of unsalvagable injury | Staff neurosurgeon, trauma surgeon OPA staff |
| I.D. of potential/eligible donors | |
| Declaration of brain death | Neurosurgery, critical care, trauma aurgery |
| Management of medical problems | Trauma surgeon, critical care, OPA staff<br>Donor management protocols |
| Obtaining consent | OPA staff<br>Primary physician<br>Social Work<br>Clergy consent 'team' |
| Operative organ harvest | Available operating room(s)<br>Transplant surgeons<br>Coordination w/other transplant centers receiving organs |

OPA, organ procurement agency; I.D., identification.

demonstrating anatomic derangements consistent with the clinical examination (head computed tomography scans), and lack of any reversible factors that might act to depress otherwise minimal brain function (hypothermia, drugs, hypotension, and so on). Cessation of brain function may be documented either by clinical examination demonstrating absent cerebral, midbrain, and brainstem functions or by angiography/nuclear flow studies documenting the absence of intracranial blood flow.

Because of the extremely short survival time of many eligible donors, the possibility of brain death should be entertained early in the hospital course, and frequent monitoring, including clinical examination and apnea testing (absent ventilatory effort in the face of hypercapnea), should be undertaken.

### *Physiologic Problems in Management of Potential Donors*

A large proportion of potential donors will exhibit severe derangements in cardiovascular, hematologic, and renal function. Even short delays in identification, neurologic evaluation/brain death declaration, tissue blood typing, obtaining consent/identifying next of kin, or harvest will result in increased procurement failure rates. The rapidity with which cardiovascular death occurs after fatal head injury serves to underscore this fact (Fig. 2).

Potential donors present a formidable challenge in terms of physiologic maintenance. Hypotension was found to be the most common and troublesome problem in this and in previous studies.[19] Although most patients were treated with dopamine and sometimes with neosynephrine, recent work demonstrated that arginine vasopressin may have increased efficacy in the hemodynamic maintenance of potential organ donors.[20] More recently we established protocols for the use of this agent.

The combined incidence of hypotension, hypothermia (poikilothermia), pulmonary edema, coagulopathy, and massive diuresis (diabetes insipidus) in patients sustaining fatal head injuries was not reported previously, but several studies noted the high individual incidence of these problems in patients with severe head injuries.[21-24] The successful management of these problems is extremely labor intensive and is best carried out in a critical care unit where interest and expertise exists. Active rewarming, massive volume replacement, ventilatory support, and aggressive treatment of hypotension will reduce the number of patients who die before completion of the procurement process.

### *Failure to Obtain Consent*

Denial of consent by next of kin was found to be the single largest cause for eligible organ procurement failure, with 46% of requests for organs denied. Previous studies reported similarly high denial rates.[13,16] Problems of consent for organ donation originally were addressed by the Uniform Anatomic Gift Act, passed in 1970.[25] Although this law establishes a legal foundation by which organ donations can be made, it makes no provisions for routine documentation of donation preferences. More recently required request laws may act to improve the frequency with which next of kin are approached regarding organ donation but they do not address the issue of consent.

Several studies have reported 50% to 80% of public survey respondents indicate their willingness to donate organs.[26,27] The 54% overall consent rate reported here is consistent with these reports. The strong ethnic bias against organ donation, particularly in the black population (Table 3), also was recognized previously. The specific reasons for this bias may be related to lack of information regarding organ transplant, distrust of the medical community, and the ethnicity (predominately white) of recipient groups.[28]

Proposed solutions to the consent problem include better education/public information regarding organ donation, increased use of donor cards, and even the adoption of a policy of 'presumed consent.' Overcast et al.[14] concluded, in a review of donor cards, that their use did not increase substantially the supply of donor organs. Only 1.7% to 8.5% of licensed drivers were found to be designated as donors in that study. In addition, although the Uniform Anatomic Gift Act grants the donee (physician or institution) the ability to act in accordance with the decedent's wishes as expressed by the donor card, few, if any, institutions are willing to pursue this line of action when it involves a conflict with the patient's next of kin.[14]

One solution to the problem of donor card use or other binding documentation would require that an individual, at the time of vehicular licensure, sign a legally valid document either granting or denying organ donation under the appropriate circumstances. With this information on record and available to organ procurement agencies, timely and appropriate decisions regarding organ donation could be made. With the majority of potential organ donors sustaining injury in vehicular accidents (55%), such a policy could have affected favorably 12 patients in this study, including an additional 3 of the 4 patients who were declared brain dead who died pending a diligent search for next of kin (Fig. 2).

The practice of presumed consent, as exists in several European countries,[29] places the responsibility for objection to organ donation on the next of kin. Such a policy would conflict with long-established legal and ethical practices and is unlikely to be adopted in the United States in the near future.

### *Recipient Renal Graft Function*

Although victims of traumatic brain injury provide a large portion of donor organs in many organ procurement programs, little follow-up data previously was available on organs harvested exclusively from trauma victims. Our data demonstrates a 23-month overall renal allograft survival rate of 77%, which is comparable to that reported in previous studies.[30,31] Patients who eventually donated kidneys had a similar incidence of pulmonary edema, coagulopathy, hypothermia, and diabetes insipidus as did the group as a whole. The observed high graft survival rates suggest that these factors do not adversely affect recipient graft function. Cecka and Terasaki,[32] in study of regraft results, even suggested that the use of cadaver kidneys from head injury victims could increase significantly renal allograft survival.

Sustained hypotension (systolic blood pressure less than 90 mmHg for more than 1 hour) and the use of high-dose pressors (dopamine more than 10 μg/kg/min) are factors that have been linked with an increased incidence of renal graft failure. Schneider et al.[33] showed an increase in acute post-transplant acute tubular necrosis associated with the use of dopamine or pitressin, and Whelchel[34] similarly showed a decrease in graft survival at 6 months in kidneys from donors receiving high-dose dopamine. We observed no such effects in this study. Patients receiving high-dose dopamine (more than 10 μg/kg/min) showed no significant differences in early or late graft function when compared to those who did not receive high-dose pressors (Table 5).

A higher graft failure rate was noted in patients who received kidneys from donors with sustained hypotension (blood pressure less than 90 mmHg for more than 1 hour) (Table 5). This is consistent with previous reports of both trauma and nontrauma donors that demonstrated significant increases in late graft failure associated with donor hypotension.[34,35] Our findings suggest that hypotension should be treated to maintain renal perfusion, even if it involves the use of higher doses of vasoactive agents.

## Summary

As organ transplant programs and recipient criteria expand, the existing shortage of donor organs will become even more acute. Traumatic injury continues to be the major source of donor organs and trauma centers are well suited to provide optimal organ procurement facilities. This analysis of organ procurement data from a level 1 center with mandatory donor identification and OPA referral demonstrates that denial of consent and inability to maintain physiologic support of potential donors constitute the two principal causes of procurement failure. Organ retrieval in this severely compromised group of patients will depend on rapid initiation and completion of the organ procurement process.

The favorable renal allograft survival rate supports aggressive resuscitation and physiologic support of potential donors with fatal head injuries. Hypotension, a frequent problem in potential donors, should be treated aggressively, with vasopressors if necessary, to maximize late renal allograft function.

## References

1. Evans RW, Manninen DL, Garrison LP, et al. Donor availability as the primary determent of the future of heart transplantation. JAMA 1986; 255:1892–1898.
2. Stuart FP. Need, supply and legal issues related to organ transplantation in the United States. Transplant Proc 1984; 16:87–94.
3. Jenkins AM. Causes of failure to harvest cadaver kidneys for transplantation. Br Med J 1976; 1:816–817.
4. Bart KJ, Macon EJ, Humphries AL, et al. Increasing the supply of cadaveric kidneys for transplantation. Transplantation 1981; 31: 383–887.
5. Caplan AL, Welvang P. Are required request laws working? Altruism and the procurement of organs and tissues. Clin Transplantation 1989; 3:170–176.
6. Roloff JS, Marshall JP, Reynolds JO, et al. Kidney transplant donors. Arch Surg 1971; 103:359–362.
7. Smith CS, Novick AC, Streem AB, et al. Recent trends in organ procurement for renal transplantation at The Cleveland Clinic Foundation. Clev Clin Qtrly 1984; 51:345–348.
8. Guidelines for the determination of death: report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 1981; 246:2184–2186.
9. Belsh JM, Blatt R, Schiffman PL. Apnea testing in brain death. Arch Intern Med 1986; 146:2385–2388.
10. United Network for Organ Sharing, Richmond, VA.
11. Shackford SR, Mackersie RC, Davis JW, et al. Epidemiology and pathology of traumatic deaths occurring at a level I center in a regionalized system: the importance of secondary brain injury. J Trauma 1989; 29:1392–1397.
12. Oksa H, Pasternack A. Availability of cadaver kidneys for transplantation from brain-dead donors. Scand J Urol Nephrol 1981; 15:291–294.

13. Morris JA, Slaton J, Gibbs D. Vascular organ procurement in the trauma population. J Trauma 1989; 29:782–788.
14. Overcast TD, Evans RW, Bowen LE, et al. Problems in the identification of potential organ donors. JAMA 1984; 251:1559–1562.
15. Prottas J, Batten HL. Health professional and hospital administrator in organ procurement: attitudes, reservations, and their resolutions. Am J Public Health 1988; 78:642–645.
16. Ross SE, Nathan H, O'Malley KF. Impact of a required request law on vital organ procurement. J Trauma 1989; 29:1036.
17. Bart KJ, Macon EJ, Humpries AL. A response to the shortage of cadaveric kidneys for transplantation. Transplant Proc 1979; 11: 455–458.
18. Pitts LH. Determination of brain death. West J Med 1984; 140: 628–631.
19. Griepp RB, Stinson EB, Clark DA, et al. The cardiac donor. Surg Gynecol Obstet 1971; 133:792–798.
20. Yoshioka T, Sugimoto H, Uenishi M, et al. Prolonged hemodynamic maintenance by the combined administration of vasopressin and epinephrine in brain death: a clinical study. Neurosurgery 1986; 18:565–567.
21. Mackersie RC, Christensen JM, Pitts LH, Lewis FR. Pulmonary extravascular fluid accumulation following intracranial injury. J Trauma 1983; 23:968.
22. Kormous RL, Donato W, Hardesty RL, et al. The influence of donor organ stability and ischemia time on subsequent cardiac recipient survival. Transplant Proc 1988; 20:980–983.
23. Pondaag W. Disseminated intravascular coagulation related to outcome in head injury. Acta Neurochirugica 1979; 28(Suppl):98–102.
24. Jorgensen EO. Spinal man after brain death. Acta Neurochirurgica 1973; 28:259–273.
25. Lee PP, Kissner P. Organ donation and the uniform anatomical gift act. Surgery 1986; 100:867–875.
26. Manninen DL, Evans RW: Public attitudes and behavior regarding organ donation. JAMA 1985; 253:3111–3114.
27. Evers S, Farewell, VT, Halloran PF. Public awareness of organ donation. CMAJ 1988; 138:237–239.
28. Callender CO. Organ donation in the black population: where do we go from here? Transplantation Proceedings 1987; 29:36–40.
29. Stuart FP, Veith FJ, Cranford RE. Brain death laws and patterns of consent to remove organs for transplantation from cadavers in the United States and 28 other countries. Transplantation 1981; 13:238–244.
30. Stratta RJ, D'Alessandro AM, Hoffmann RM, et al. Cadaveric renal transplantation in the cyclosporine and OKT3 eras. Surgery 1988; 104: 606–615.
31. Lewis RM, Janney RP, Golden DL, et al. Stability of renal allograft function associated with long-term cyclosporine immunosuppressive therapy—five year follow-up. Transplantation 1989; 47: 266–272.
32. Cecka JM, Terasaki PI. Imporvement of kidney transplant regraft results by using trauma death donors. Transplantation 1987; 44: 792–795.
33. Schneider A, Toledo-Pereyra LH, Zeichner WD, et al. Effect of dopamine and pitressin on kidneys procured and harvested for transplantation. Transplantation 1983; 36:110–111.
34. Whelchel JD, Diethelm AG, Phillips MG, et al. The effect of high-dose dopamine in cadaver donor management on delayed graft function and graft survival following renal transplantation. Transplant Proc 1986; 18:523–527.
35. Toledo-Pereyra LH, Moberg AW, Callender CO, et al. Factors determining early kidney function following clinical preservation. Minn Med 1975; 58:446.

# Transvaginal Approach for Repair of Rectovaginal Fistulae Complicating Crohn's Disease

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**The management of rectovaginal fistulae complicating Crohn's disease is difficult and often unsatisfactory. Between December 1983 and November 1988, 13 patients with Crohn's disease underwent repair of rectovaginal fistulae *via* a transvaginal approach. All patients had a diverting intestinal stoma either as part of the initial step in the staged management of intractable perianal disease or concurrent with the repair of the rectovaginal fistula. Each of the patients had low or mid septal fistulae; high fistulae generally are treated transabdominally and are not the focus of this discussion. Fistulae were eradicated in 12 of the 13 women and did not recur during the follow-up period, which averaged 50 months (range, 9 to 68 months). The only treatment failure was a patient who had a markedly diseased colon from the cecum to the rectum and a very low-lying fistula. It is concluded that a modified transvaginal approach is an effective method for repair of rectovaginal fistulae secondary to Crohn's disease.**

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THE MANAGEMENT OF rectovaginal fistulae complicating Crohn's disease is a challenging surgical problem. Surgical repair of rectovaginal fistula can be attempted in a variety of ways. The approach may be abdominal, rectal, vaginal, perineal, trans-sphincteric, or trans-sacral. In 1934 Bey[1] commented that because many types of operative procedures exist for the repair of rectovaginal fistulae, it indicates no procedure is outstandingly successful. In the 50 years that passed, the literature still offers an assortment of operative approaches from which to choose.

At the turn of the century, most rectovaginal fistulae were repaired transvaginally either by converting the fistula into a fourth degree laceration and then repairing the laceration in layers[2] or by closure of the anterior rectal wall and posterior vaginal wall in layers after excising only the fistula.[3,4] However vaginal repairs have been criticized in the literature and shown to be associated with a significant recurrence rate.[2] Subsequently Laird[5] refocused the surgical literature on a transanal technique first described in 1902.[6] Laird[5] successfully used an anterior rectal mucosal flap in the treatment of low rectovaginal fistulae.

More recently several large series of patients have been reported,[7-10] where modification of the transanal approach has been used with acceptable results. However these reports fail to identify the most appropriate therapy for rectovaginal fistulae complicating Crohn's disease. Other authors[11-14] used the transanal approach for the treatment of fistulae complicating Crohn's disease but the recurrence rates have not been superior to any other surgical approach.

Crohn's disease complicates the surgical repair with characteristic poor wound healing. This may be related to both the poor healing qualities of the diseased rectum and the systemic corticosteroids with which most of these patients were treated. The diarrheal stools can make even the smallest fistula a management problem for the patient. The fistula may recur or form anew due to the transmural nature of the disease. Because the literature has not clarified the optimal management for fistulae complicating Crohn's disease, we thought that results gathered from a personal series of 13 patients managed *via* a modified transvaginal approach would be valuable. Although many authors report the use of a transvaginal approach for the repair of these complicated fistulae, none have described the raising of a vaginal flap with the interposition of the levator ani muscles. This approach may represent another swing of the pendulum because the most frequently used surgical technique of the past decade has been a transanal advancement flap.

## Clinical Material

Thirteen patients with rectovaginal fistulae complicating Crohn's disease comprise the clinical experience on which this personal series is based (Table 1). Initially all patients presented with vaginal flatus, feces, and/or discharge causing some perineal discomfort and difficulty with hygiene. Diagnostic workup included a barium enema, small bowel series, and endoscopy to define clearly the anatomy of the fistula and the extent of active disease elsewhere in the bowel. All 13 patients had Crohn's colitis. Six patients had previous bowel resections that clearly document the histopathology to be representative of Crohn's disease. The other seven patients had clinical,

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TABLE 1A. *Clinical Summary*

| Patient | Age (yrs) | Duration of Crohn's (yrs) | Extent of Disease | Location/size of RVF | T.I. Disease | Medical Therapy Preop/postop |
|---|---|---|---|---|---|---|
| 1 | 32 | 7 | C.C. + RVF | Low/3–4 mm | Yes | Azul/6 MP<br>Pred/Flagyl |
| 2 | 34 | 12 | C.C. + RVF | Low/3 mm | Yes | 6 MP/6 MP<br>Flagyl/Flagyl |
| 3 | 28 | 5 | Anorectal, C.C. + RVF | Mid/<1 cm | Yes | Pred/Azul<br>/Flagyl |
| 4 | 34 | 3 | Anorectal, C.C. + RVF, RCF | Low/<1 cm | No | Azul/Azul<br>Flagyl/Flagyl |
| 5 | 24 | 5 | C.C. + RVF, RCF | Low/<1 cm | Yes | Pred/Pred<br>Flagyl/Flagyl |
| 6 | 53 | 9 | C.C. + RVF, RCF | Mid/<1 cm | Yes | Azul/Azul<br>Flagyl/Flagyl |
| 7 | 41 | 8 | Anorectal, C.C. + RVF | Mid/<1 cm | No | Azul/Azul<br>Flagyl/Flagyl |
| 8 | 32 | 6 | Anorectal, C.C. + RVF | Mid/<1 cm | No | Azul/Azul<br>Flagyl/Flagyl |
| 9 | 44 | 23 | C.C. + RVF, RCF | Low/<1 cm | No | 6 MP/6 MP<br>Flagyl/Flagyl |
| 10 | 50 | 6 | C.C. + RVF | Low/>2.5 cm | No | Azul/Azul<br>Flagyl/Flagyl<br>Pred/ |
| 11 | 28 | 6 | C.C. + RVF | Mid/<1 cm | No | Azul/Azul<br>Flagyl/Flagyl |
| 12 | 34 | 10 | Pancolitis + RVF | Very/<1 cm low/ | No | Azul/Azul<br>Pred/6 MP<br>/Flagyl |
| 13 | 49 | 21 | C.C. + RVF | Mid/<1 cm | Yes | Azul/Azul<br>Flagyl/Flagyl<br>Pred/ |
| Mean | 37.2 | 9.3 | — | — | 6/13 | — |

RVF, rectovaginal fistula; Azul, azulfidine; RCF, rectocutaneous fistula; Pred, prednisone; ICF, ileocutaneous fistula; 6 MP, 6 mercaptopurine; T.I., terminal ileum; C.C., Crohn's colitis.

radiographic, and endoscopic findings consistent with the diagnosis of Crohn's disease. In addition the pathology report in three of the seven patients revealed the typical signs of Crohn's disease, including granulomata. In the other four patients (numbers 4, 7, 8, and 11), anorectal disease with a rectovaginal fistula constituted the only evidence of pathologic bowel. We thought a full-thickness biopsy of the fistula site in these four patients would only enlarge the defect and increase the chance for failure. Nevertheless we were convinced from clinical, radiographic, and endoscopic findings that these patients had Crohn's disease.

Medical therapy before rectovaginal fistulae repair included sulfasalazine, metronidazole, 6-mercaptopurine (6MP), 5-aminosalicylic acid (5-ASA) enemas, and methylprednisolone. Seven patients were never treated with corticosteroids. The other six patients were tapered off methylprednisolone in anticipation of fistula repair. Only one patient (number 5) remained on corticosteroids after operation. Four patients used 6MP after operation.

Between December 1983 and November 1988, we operated on 13 women with rectovaginal fistulae complicating Crohn's disease. All patients had the typical endoscopic appearance of Crohn's disease with patchy, asymmetric lesions and some with deep linear ulcers in the rectum and sigmoid colon. All 13 patients had low or mid rectovaginal fistulae and all but one measured less than 1 cm in diameter. In this patient (number 10), the fistula was so extensive following recurrent infections that the distal portion of the rectovaginal septum was obliterated. In addition to the rectovaginal fistulae, three patients (numbers 4, 5, and 9) each had a rectocutaneous fistula and one patient (number 6) had an ileocutaneous fistula.

The mean age of the women at the time of repair was 37.2 years (range, 24 to 53 years). The average duration of Crohn's disease before the fistulae occurred was 9.3 years (range, 5 to 23 years). Three of the thirteen patients had previous attempts at repair of the rectovaginal fistulae, two *via* a transvaginal approach and one *via* a transanal approach. All patients had a staged diverting intestinal stoma either before or concurrent with the repair of the fistulae.

## Operative Technique

Following the administration of a general anesthetic, the patient was placed in a lithotomy position and the

TABLE 1B. *Clinical Summary*

| Patient | Past Surgical History | Surgical Procedure | Diversion | Follow-up |
|---|---|---|---|---|
| 1 | Subtotal colectomy, ileosigmoidostomy, ileostomy | MTV-RVF repair | P | Healed<br>68 mos. |
| 2 | Transvaginal RVF repair, diverting loop ileostomy | MTV-RVF repair | P | Healed<br>67 mos. |
| 3 | — | MTV-RVF repair | C | Healed<br>66 mos. |
| 4 | — | MTV-RVF repair | C | Healed<br>64 mos. |
| 5 | Subtotal colectomy, ileosigmoidostomy, ileostomy | MTV-RVF repair, vaginoplasty | P | Healed<br>62 mos. |
| 6 | Fistulectomy, partial colectomy, transanal RVF repair | MTV-RVF repair, division of ICF, ileal resection | C | Healed<br>62 mos. |
| 7 | — | MTV-RVF repair | C | Healed<br>59 mos. |
| 8 | — | MTV-RVF repair | C | Healed<br>58 mos. |
| 9 | Subtotal colectomy, ileosigmoidostomy, ileostomy | MTV-RVF repair | P | Healed<br>46 mos. |
| 10 | Diverting split-transverse colostomy | MTV-RVF repair, posterior colporrhaphy | C | Healed<br>37 mos. |
| 11 | Ileocolic resection | MTV-RVF repair | C | Healed<br>36 mos. |
| 12 | Transvaginal RVF repair, diverting loop ileostomy | MTV-RVF repair | P | Failed<br>16 mos. |
| 13 | Ileocolic resection | MTV-RVF repair, secondary ileocolic resection | C | Healed<br>9 mos. |
| Mean | — | — | P 5/13<br>C 8/13 | 12/13 Healed<br>50.0 mos. |

MTV-RVF repair, modified transvaginal rectovaginal fistula repair; ICF, ileocutaneous fistula; P, before the repair; C, concurrent with the repair.

rectovaginal fistula identified. An incision was made in the posterior vaginal wall around the introitus and a vaginal flap raised (Fig. 1), from the apex to the base, exposing the attenuated septum and perineal body. The flap was wide to assure adequate vascular supply. Dissection was extended laterally and posteriorly to the ischial tuberosities for the purpose of releasing tension. Meticulous hemostasis was achieved. The vaginal and rectal defects were identified and repaired with absorbable sutures (Fig. 2). The levator ani muscles were approximated in the midline without tension (Fig. 3). This was crucial to the repair. The levator ani muscles were sutured between the rectal and vaginal walls with #0 absorbable interrupted sutures for the purpose of separating the already-sutured rectal and vaginal defects. The vaginal flap was advanced over the repaired area. Excess vaginal flap, including the vaginal fistula site, was excised. The flap was sutured to the perineal skin with absorbable sutures (Fig. 4). If not already present, a proximal diverting loop ileostomy was performed concurrent with the repair.

## Results

The operative and postoperative courses are summarized in Tables 1A and B. All patients underwent repair as previously described. There were no operative deaths. Rectovaginal fistulae were eradicated in 12 of the 13 patients. This represents a 92.3% cure rate. Follow-up data was obtained by office examination or by telephone interview up to 5.5 years after operation. The follow-up period ranged from 9 to 68 months, with an average follow-up period of 50 months. All 13 patients had fecal diversion. Five patients had fecal diversion before the repair of the rectovaginal fistulae and eight patients had a diverting stoma performed concurrent with the transvaginal repair. Intestinal continuity was restored in 12 patients; the one patient that still has a stoma (number 12) represents our only treatment failure. In the other 12 patients the rectovaginal fistulae healed with total eradication of the tract and associated symptoms. In this series no patient required a total proctocolectomy and the anal sphincter mechanism was undisturbed, leaving all patients continent for feces and flatus.

We performed a full-thickness biopsy of the fistula site in six patients. The pathology report of three fistulae specimens revealed fibrosis and nonspecific chronic inflammation of the vaginal mucosa and skin. The other three specimens had granulomata but no signs of malignancy.

During the follow-up period the only complication was an incisional hernia in patient 9. Patient 2 experienced

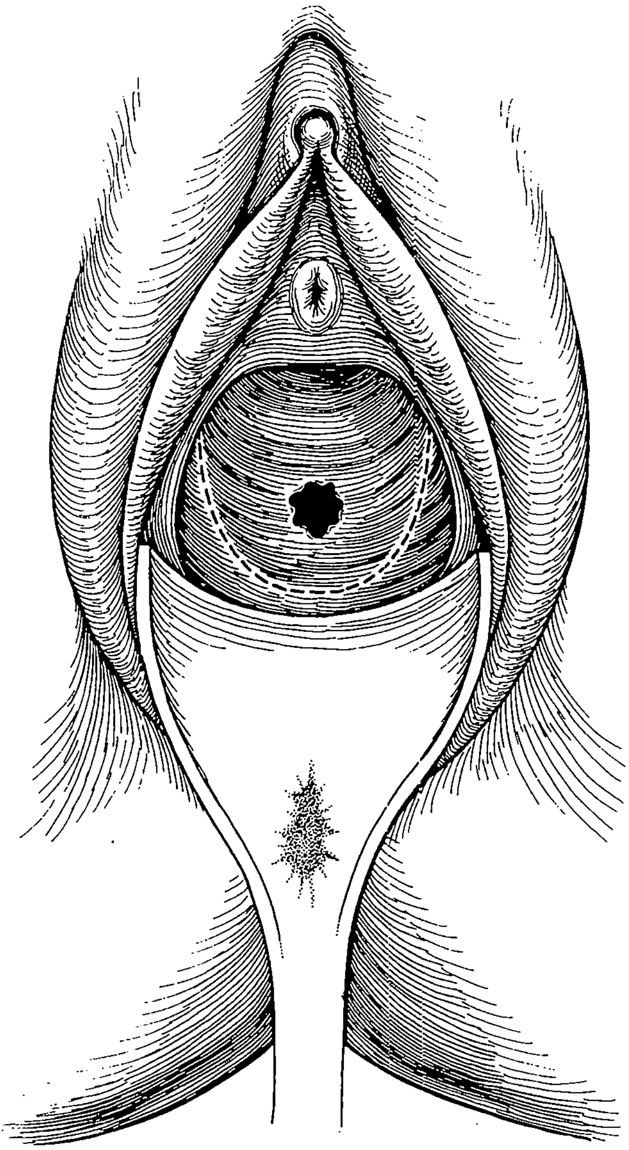

FIG. 1. A transvaginal view of the rectovaginal fistula. The dotted line represents the line of incision.

transient dyspareunia lasting 2 months. Patient 1 became pregnant 3 years after her repair and delivered vaginally without complications or breakdown of the repair.

In general operative repair was followed by traditional medical treatment. All patients were tapered off corticosteroids, if previously maintained on them. 6-mercaptopurine was used to control the underlying intestinal disease and decrease the need for corticosteroids. In three patients the corticosteroids were discontinued without the addition of 6MP. Only one patient remained on corticosteroids after operation. She could not tolerate the adverse effects of 6MP; however the healing of her fistula was not affected. Four patients were maintained on 6MP after operation and none of them required corticosteroids. Metronidazole, sulfasalazine, and 5-ASA were symptomatically helpful in some patients.

## Discussion

Rectovaginal fistulae are relatively uncommon. They account for less than 5% of fistula originating in the anorectum.[5] Surgical and obstetric injuries remain the most frequent causes.[15] Other etiologies include an imperforate anus, irradiation-induced damage, tuberculosis, Bartholin's abscess, and inflammatory bowel disease. The exact incidence of rectovaginal fistula in Crohn's disease is unknown; data varying from 0.91% to 18% are reported in the literature.[16,17] In 1958 Crohn and Yarnis[18] reported a 1.6% incidence of rectovaginal fistulae in 542 cases of regional ileitis. The lowest incidence of rectovaginal fistulae associated with Crohn's disease (0.91%) was reported by Hightower et al.[16] in a series of 220 patients with colitis. A recent study by Radcliff of 886 women with Crohn's disease and intact distal large bowel reported that 1 in 10 women with Crohn's disease develop a rectovaginal fistula.[14] In our limited series, we were unable to comment on the incidence.

Perianal disorders, including fistulae, abscesses, fissures, and edematous cyanotic anal skin tags frequently complicate inflammatory bowel disease and may be recognized as a hallmark of Crohn's disease. Tuxen an Castro[19] re-

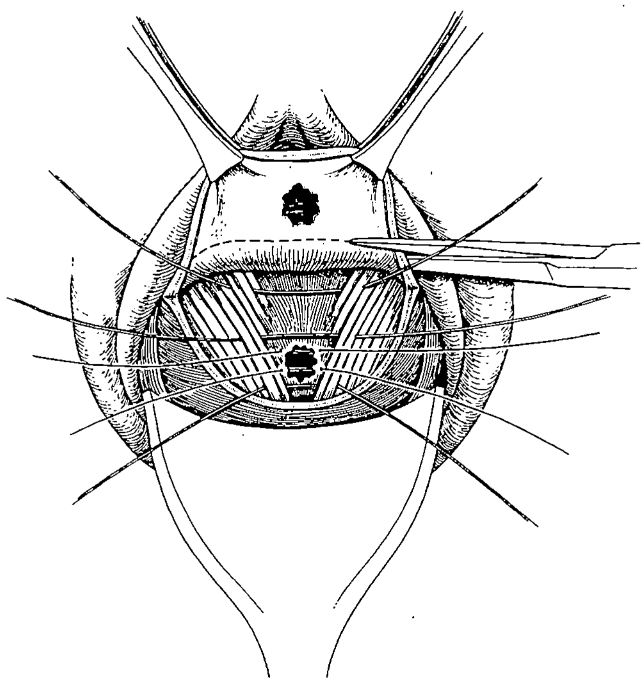

FIG. 2. The vaginal flap has been raised. Excess flap is excised. The vaginal side of the fistula opening is shown. The rectal side of the fistula is closed with absorbable sutures. Sutures to approximate the levator ani muscles are placed.

ported a 25% to 50% incidence of perianal disorders in all cases of Crohn's disease. A higher incidence of perianal and perineal involvement is associated with 'colonic' Crohn's disease than regional ileitis.[20] Bagby et al.[21] also noted that rectovaginal fistula developed more commonly in Crohn's patients with severe colonic involvement. This association has been confirmed by many authors.[12,14] In our series all 13 women had Crohn's colitis and four of them had only anorectal disease. All 13 patients had some perianal involvement. This helped us distinguish between ulcerative colitis and Crohn's disease in the four patients without pathologic proved specimens. We intentionally did not take a full-thickness biopsy of the rectum or rectal fistula site for further confirmation of Crohn's disease. We thought that unnecessary manipulation and instrumentation of the diseased rectum would only enlarge the defect, make it more difficult to close primarily, and increase the chance for failure of fistula repair.

There was no association between disease in the distal ileum and failure of the fistula repair. Patients with ileocolic disease have a high incidence of recurrence of Crohn's disease,[22] but there is no evidence to support any relationship between ileocolic disease and failure of rectovaginal fistula repair.

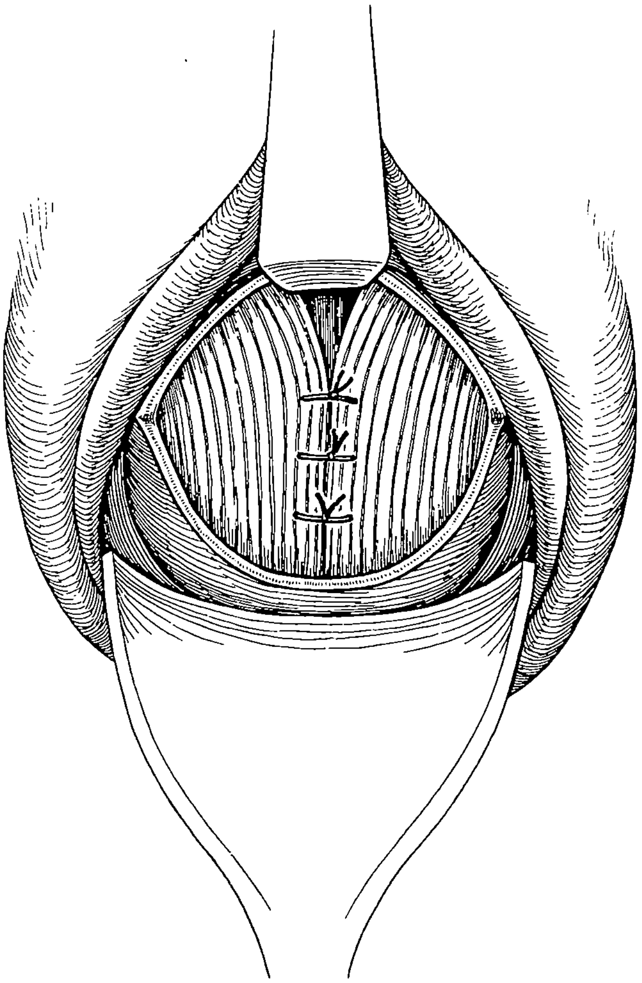

FIG. 3. The levator ani muscles are approximated so that they are interposed between the rectal and vaginal walls.

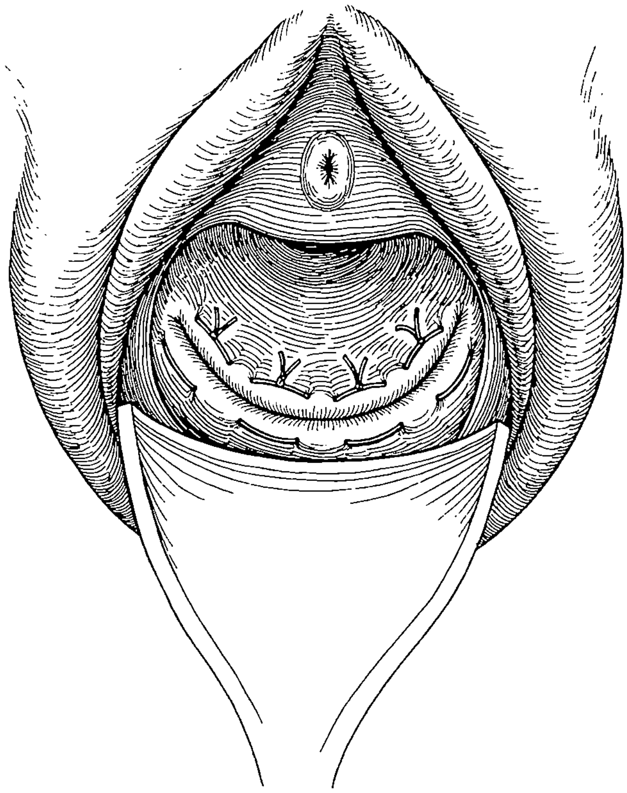

FIG. 4. The vaginal mucosal flap is advanced and sewn to the perineum with absorbable sutures.

The surgical management of rectovaginal fistulae in Crohn's disease has been associated with unacceptable recurrence rates. Some authors emphasize the futility and danger of a local repair.[19,23-25] Goligher[23] suggests that abdominoperineal resection is the gold standard for patients with rectovaginal fistula and colitis. Nevertheless, in this decade, a trend toward rectal preservation has evolved.[22] In addition, because a rectovaginal fistula was the only manifestation of Crohn's disease in some of our patients, we thought that an abdominal perineal resection was too high a price to pay for such localized disease. Currently most surgeons accept the use of local operations in selected patients.[7,11,26,27]

In 1979 Tuxen and Castro[19] proposed four acceptable alternatives in the treatment of a rectovaginal fistula in Crohn's disease. They include (1) medical treatment with adequate drainage to control infection; (2) proximal diversion of fecal stream with or without intestinal resection; (3) abdominoperineal resection of the rectum and closure of the vaginal fistula with the creation of a permanent ostomy; and (4) local closure of the fistula by a myriad of approaches.

Medical management is tedious and suboptimal. Medical therapy may alleviate symptoms but rarely results in spontaneous complete or sustained healing of fistulae.[25,28] Buls and Rothenberger[15] have reported only one patient who achieved healing on immunosuppressive therapy. Alternatively the use of immunosuppressive agents may eliminate the need for corticosteroids. Four patients were maintained on 6MP and none of them required continued use of corticosteroids. Only one patient continued to take 10 mg of methylprednisolone after operation. Her fistula and perineum healed completely, but at a slower rate.

Medical therapy is aimed at treating the underlying intestinal disorder, malnutrition, infection, and controlling the diarrhea. Corticosteroids, hyperalimentation, low-residue diets, sulfasalazine, and 5-ASA enemas were all useful in the treatment of our patients but had no effect on the rectovaginal fistula. Recently Bernstein and associates[29] reported encouraging results in 21 patients treated with long-term metronidazole. Symptomatic improvement occurred in all patients and a small group of patients had complete healing of the fistula. Fry et al.[12] also believed that metronidazole was beneficial for the healing of perianal disease. We used metronidazole with all of our patients. It also has been suggested that sulfasalazine facilitates healing of anorectal wounds.[30] However the efficacy of medical therapy requires further documentation.

The method of operative repair will vary with respect to location, size, and etiology of the fistula. Of these factors, the etiology is the primary determinant in selecting an appropriate repair.[15] Buls and Rothenberger[15] classified fistulae with an etiology due to inflammatory bowel disease, malignancy, or irradiation as complex. Fistulae secondary to trauma or infection are considered simple. He further grouped these fistulae according to size and location. A fistula measuring less than 2.5 cm in diameter and one that was in a low or mid septal location also was considered simple. For convenience many surgeons arbitrarily classify a fistula as low if it can be surgically corrected from a perineal approach. In our series all patients had low and mid fistulae and only one patient had a defect larger than 2.5 cm. Nevertheless size and location did not play a role in choosing an operative procedure because all of our patients had clinical, radiologic, and pathologic findings that strongly suggested Crohn's disease.

We used a transvaginal approach on all of our patients. The primary advantage is the use of nondiseased, pliable, and intact vaginal tissue in forming the flap, with minimal manipulation and instrumentation of the diseased rectum. We also interpose the levator ani muscles between the rectal and vaginal mucosal wall. This provides support to the septum and separates the rectal and vaginal suture lines, thereby reducing the possibility of a recurrence. The only failure in our series (patient 12) was related to this portion of the operation. The fistula was so low that approximating the levator ani muscles did not separate the rectal and vaginal walls in the area of the fourchette. Repair of this fistula failed and the diverting stoma is still in place and functioning. The lack of levator ani support anteriorly in this patient resulted in a compound tracking anoperineal fistula. Eight months later, at another institution, this patient underwent another operation for this anoperineal fistula. Her repair consisted of excision of the fistula with a lateral side-to-side mucosal advancement flap. She remains asymptomatic and without a recurrence during a 3-month follow-up period.

Before the onset of this study, we treated one patient (number 2) *via* a transvaginal approach; however a different technique was used. The repair did not consist of the interposition of the levator ani muscles between the rectal and vaginal walls. This repair failed. Consequently we modified our technique by interposing the levator ani muscles in all rectovaginal septal repairs. This patient was reoperated on with the modified transvaginal approach and the rectovaginal fistula healed in this patient without a recurrence during a 67-month follow-up period. The vaginal approach also allows wide mobilization of normal mucosa. It also eliminates the possibility of fecal incontinence because the sphincters are not disturbed. Hudson[31] reports the least risk of rectal stricture with a vaginal approach. It is essential to achieve a good anatomic repair free of tension and with a well-vascularized vaginal flap. We report no incidence of postoperative infection or necrosis of the flap. This is the most common complication of a transanal approach.[4] Because we advance a vaginal flap, a possible complication is shortening the vagina with resulting dyspareunia. Patient 2 complained of transient dyspareunia after operation that lasted approximately 2 months until the vagina dilated. This may have been the consequence of multiple transvaginal advancement flap repairs; however only the most recent repair included the interposition of the levator ani muscles and resulted in a healed perineum.

Using a transanal rectal advancement flap, Jones and Fazio[11] treated 10 patients with Crohn's disease and a rectovaginal fistula and obtained a 40% recurrence rate. Radcliff and associates[14] treated 11 patients by transanal repair. Five patients underwent transanal anterior rectal flap technique with two recurrences, and in six patients an endoanal flap advancement technique was used with two recurrences. Therefore their total transanal recurrence rate was 36.4%. In a 1989 Fry et al.[12] reported a recurrence in one of three patients treated by an endorectal advancement flap technique.

The endorectal advancement flap technique has experienced success with simple rectovaginal fistulae (excluding inflammatory bowel disease). However documented success of this endorectal advancement flap technique with Crohn's disease is lacking. The literature estimates a 30% to 40% recurrence rate for patients with complex fistulae, treated by this technique (Table 2). An anecdotal report by Farkas and Gingold[27] comment on only one case successfully treated with this technique.

Crohn's disease challenges the skill of the surgeon. These patients exhibit poor wound healing, require corticosteroids for the treatment of their disease, and usually have had recurrent abscess formation and the reformation of the fistula during the course of their disease.[25] For these reasons a diverting stoma is a necessary accompaniment to the surgical repair of the rectovaginal fistulae.

All 13 of our patients underwent a temporary diverting stoma at some time before or concurrent with the fistula repair. Five patients underwent fecal diversion before the repair and eight patients had diverting stomas concurrent with the repair. Three of the five ostomies were performed before the repair as part of a staging procedure. The other two patients underwent fecal diversion at previous unsuccessful attempts at repair of the rectovaginal fistulae. The three patients who were staged underwent subtotal colectomies, ileosigmoidostomies, and diverting loop ileostomies for extensive perianal Crohn's disease intractable to medical therapy. The second stage of the procedure consisted of the modified transvaginal fistulae repair a few months later.

Fecal diversion serves three purposes. First it diverts the fecal stream away from the healing perineum. Second it may have a beneficial effect on the local disease by improvement in the proximal intestinal disease. Harper et al.[38] showed that patients with colonic Crohn's disease improve clinically when the colon is defunctional. Third, if the repair fails and the resulting defect is larger, mucus but no fecal material will be discharged through the vagina.

Tuxen and Castro[19] comment that after proximal diversion alone, symptoms may decrease, but the fistula tract usually remains patent and epithelialized. Fry and associates[13] also report that diversion of the fecal stream, by itself, is unsuccessful in healing the rectal lesions. Nevertheless they found that 11 of 14 patients treated by fecal diversion accompanied by a local anorectal operation had an improvement in the perianal disease. Other authors support this concept[23,24] while others emphatically refute it.[14,17] Despite this controversy we found it prudent to use a stoma as an initial step in the management of these patients. Block[39] advocates a graded policy of management determined by the presence or absence of rectal disease. If the rectum is not involved, the rectovaginal fistulae is treated without diversion, but when involved he recommends the use of fecal diversion as a preliminary pro-

TABLE 2. *Historical Summary of Results of Rectovaginal Fistulae Repairs*

| Author (Reference) | Approach | No. of Patients | No. of Failures | Failure Rate (%) | Etiology of RVF |
|---|---|---|---|---|---|
| Lescher (2) | V | 49 | 8 | 16.3 | S |
| Given (3) | V | 25 | 3 | 12.0 | S |
| Lawson (32) | V | 53 | 11 | 20.8 | S |
| Total | V | 127 | 22 | 17.3 | S |
| Russell (7) | A | 21 | 6 | 28.6 | S |
| Hoexter (8) | A | 15 | 0 | 0.0 | S |
| Rothenberger (9) | A | 35 | 5 | 14.3 | S |
| Hilsabek (10) | A | 9 | 0 | 0.0 | S |
| Greenwald (34) | A | 20 | 0 | 0.0 | S |
| Rothenberger (35) | A | 40 | 5 | 12.5 | S |
| Jackman (36) | A | 15 | 0 | 0.0 | S |
| Gallagher (37) | A | 20 | 1 | 5.0 | S |
| Total | A | 175 | 17 | 9.7 | S |
| Bandy (33) | V | 10 | 3 | 30.0 | C |
| Jones (11) | A | 10 | 4 | 40.0 | C |
| Fry (12) | A | 3 | 1 | 33.3 | C |
| Fry (13) | A | 10 | 3 | 30.0 | C |
| Radcliff (14) | A | 11 | 4 | 36.4 | C |
| Farkas (27) | A | 1 | 0 | 0.0 | C |
| Total | A | 35 | 12 | 34.3 | C |
| Present series | MTV | 13 | 1 | 7.7 | C |

A, anal; V, vaginal; MTV, modified transvaginal; RVF, rectovaginal fistula; S, simple, simple etiology includes those of infectious or traumatic origin; C, complex, complex etiology includes those of Inflammatory Bowel Disease, malignancy or radiation damage.

cedure before treating the rectovaginal fistula. In all of our cases the rectum was involved and we thought it essential to use a defunctioning stoma and a transvaginal approach. We think the diseased rectum precludes the use of a transanal approach.

## Conclusion

The management of rectovaginal fistulae in Crohn's disease is a challenging problem. Regardless of the approach or surgical technique for repair, certain principles have been taught and must be upheld.[1,9] They include precise anatomic identification of the fistula, elucidation of the etiology, gentle dissection with careful hemostasis, full mobilization, accurate apposition of healthy tissue without tension, adequate vascularization, excision of the tract, followed by a layered meticulous closure. The diverting stoma is thought to be essential. We think a transvaginal approach has many advantages and adheres to all of the basic principles. We report a 92.3% cure rate with our technique in the treatment of rectovaginal fistulae complicating Crohn's disease. The excellent results in our patients may be attributed in part to previous excision of diseased bowel, the use of a temporary diverting stoma, the interposition of the levator ani muscle wall, and primarily the use of the transvaginal approach, which allows for the mobilization of healthy tissue in repairing the defect.

## References

1. Bey NM. A new technique in dealing with superior rectovaginal fistulae. J Obstet Gynecol 1934; 41:579–587.
2. Lescher TC, Pratt JH. Vaginal repair of the simple rectovaginal fistula. Surg Gynecol Obstet 1967; 124:1317–1321.
3. Given FT. Rectovaginal fistula: a review of 20 years' experience in community hospital, Am J Obstet Gynecol 1970; 108:41–46.
4. Daniels BT. Rectovaginal fistula: a clinical and pathological study. Doctoral dissertation. Minneapolis: University of Minnesota Graduate School, 1949.
5. Laird DR. Procedures used in treatment of complicated fistulas. Am J Surg 1948; 76:701–708.
6. Noble GH. A new operation for complete laceration of the perineum designed for the purpose of eliminating danger of infection from the rectum. Trans Am Gynecol Soc 1902; 27:357–363.
7. Russell TR, Gallagher DM. Low rectovaginal fistulas: approach and treatment. Am J Surg 1977, 134:13–17.
8. Hoexter B, Labow SB, Moseson MD. Transanal rectovaginal fistula repair. Dis Colon Rectum, 1985; 28:572–575.
9. Rothenberger DA, Christenson MD, Balcos EG, et al. Endorectal advancement flap for treatment of simple rectovaginal fistula. Dis Colon Rectum 1982; 25:297–300.
10. Hilsabek JR. Transanal advancement of the anterior rectal wall for vaginal fistulas involving the lower rectum. Dis Colon Rectum 1980; 23:236–241.
11. Jones IT, Fazio VW, Jagelman DG. The use of transanal rectal advancement flaps in the management of fistulas involving the anorectum. Dis Colon Rectum 1987; 30:919–923.
12. Fry D, Shemesh EI, Kodner IJ, et al. Techniques and results in the management of anal and penianal Crohn's disease. Surg Gynecol Obstet 1989; 168:42–28.
13. Fry RD, Koder IJ. Management of anal and penineal Crohn's disease. Infections in Surg 1989; 9:209–220.
14. Radcliff AG, Ritchie JK, Hawley PR, et al. Anovaginal and rectovaginal fistulas in Crohn's disease. Dis Colon Rectum 1988; 31: 91–94.
15. Buls JG, Rothenberger DA. Anal and rectovaginal fistulas: repair of the low fistula. *In* Kodner IJ, Fry RD, Roe JP, eds. Colon, Rectal and Anal Surgery: Current Techniques and Controversies. St. Louis: CV Mosby, 1985; pp 63–75.
16. Hightower NC Jr, Broders AC Jr, Haines RD, et al. Chronic ulcerative colitis. Am J Dig Dis 1958; 3:722.
17. Ritchie JK, Lennard-Jones JE. Crohn's disease of the distal large bowel. Scand J Gastroent 1976; 11:433–436.
18. Crohn BB, Yarnis H. Regional Iletits, Second Edition. New York: Grune and Stratton Inc., 1958.
19. Tuxen PA, Castro AF. Rectovaginal fistula in Crohn's disease. Dis Colon Rectum 1979; 22:58–62.
20. Greenstein AJ, Kark AE, Dreiling DA. Crohn's disease of the colon. Am J Gastroenterol 1974; 62:419–429.
21. Bagby RJ, Clements JL, Patrick JW. Genitourinary complications of granulomatous bowel disease. Am J Roentgenol Radium Ther Nucl Med 1973; 117:297–303.
22. Wolff BG, Culp CE, Beart RT Jr, et al. Anorectal Crohns disease—a long term perspective. Dis Colon Rectum 1985; 28:709–711.
23. Goligher JC. Rectovaginal fistula and irradiation procitis and enteritis. *In* Goligher JC, et al. Surgery of the Anus, Rectum, and Colon. Springfield, IL: Charles C. Thomas, 1975, pp 827–852.
24. Givel JC, Hawker P, Allan RN, et al. Enterovaginal fistulas associated with Crohn's disease. Surg Obstet Gynecol 1982; 155:494–496.
25. Faulconer HT, Muldoon JP. Rectovaginal fistula in patients with colitis: review and report of a case. Dis Colon Rectum 1975; 18: 413–415.
26. Greenstein AJ. The surgery of Crohn's disease. Surg Clin North Am 1987; 67:573–595.
27. Farkas AM, Gingold BS. Repair of rectovaginal fistula in Crohn's disease by rectal mucosal advancement flap. Mt Sinai J Med 1983, 50:420–423.
28. Holland RM, Greiss FC. Perineal Crohn's disease. Obstet Gynecol 1983; 62:527–529.
29. Bernstein LH, Frank MS, Brandt LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. Gastroenterology 1980; 79: 357–365.
30. Hellers G, Bergstrand O, Ewerth S, Holmstrom B. Occurence and outcome after primary treatment of anal fistulae in Crohn's disease. Gut 1980; 21:525–527.
31. Hudson CN. Rectovaginal and other fistulae between the intestine and genital tract. *In* Rob C, Smith R, eds. Operative Surgery: Colon, Rectum and Anus, Third Edition. London: Butterworth & Company, 1977.
32. Lawson J. Rectovaginal fistulae following difficult labour. Proc R Soc Med 1972; 65:283.
33. Bandy LC, Addison A, Parker RT. Surgical management of rectovaginal fistulas in Crohn's disease. Am J Obstet Gynecol 1983; 147:359–363.
34. Greenmwald JC, Hoexter B. Repair of rectovaginal fistulae. Surg Gynecol Obstet 1978; 146:443–445.
35. Rothenberger DA, Goldberg SM. The management of rectovaginal fistulae. Surg Clin North Am 1983; 63:61–79.
36. Jackman RJ. Rectovaginal and anovaginal fistulas: a surgical procedure for the treatment of certain types. J Iowa St Med Soc 1952; 42:435–440.
37. Gallagher DM, Scarborough RA. Repair of low rectovaginal fistula. Dis Colon Rectum 1962; 5:193–195.
38. Harper PH, Kettlewell MGW, Lee ECG. The effect of split ileostomy on Crohn's disease. Br J Surg 1982; 69:608–610.
39. Block IR, Rodriquez S, Olivares AL. The Warren operation for anal incontinence caused by disruption of the anterior segment of the anal sphincter, perineal body and rectovaginal septum: report of five cases. Dis Colon Rectum 1975; 18:28.

# Glucose Metabolism After Pancreas Autotransplantation

## *The Effect of Open Duct* Versus *Urinary Bladder Drainage Technique*

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**Glucose metabolism and insulin secretion after pancreas transplantation may be affected by the technique used for ductal drainage. We evaluated peripheral glucose and insulin levels after oral (oral glucose tolerance test [OGTT]) and sustained stable hyperglycemic challenge (clamp) in dogs who had undergone pancreas autotransplantation with intraperitoneal drainage (PAT) or with urinary bladder to pancreatic duct anastomosis (PAT/B). Both groups had basal glucose values comparable to normal controls; PAT/B animals had fasting hyperinsulinemia. Pancreas autotransplantation animals had an increased integrated glucose response to OGTT and blunted insulin response to hyperglycemic clamp. Urinary bladder to pancreatic duct anastomosis animals had a significantly decreased integrated glucose response to OGTT compared to PAT and an exaggerated insulin response to hyperglycemic challenge, which approximated normal control values by the last 30-minute period of the clamp. Interestingly M values, which approximate glucose metabolized during the hyperglycemic challenge, were depressed in both surgical groups. It is concluded that the technique of bladder drainage allows a 'normalization' of peripheral levels of insulin that is associated with amelioration of an altered glucose response after oral challenge. However the clamp studies show that, despite the improvement in insulin response, an insensitivity may exist to a wide range of endogenous levels after pancreas transplantation.**

CLINICAL PANCREATIC ALLOTRANSPLANTATION has been used with increasing frequency for treatment of patients with type I diabetes.[1,2] The anatomic changes that accompany surgical manipulation of the pancreas graft, which subsequently is revascularized, as opposed to islet cell harvesting, might be predicted to have important consequences on postoperative glucose metabolism. Three important surgical alterations include (1) reduction of beta cell mass by use of segmental transplantation or due to preservation techniques, (2) systemic drainage of pancreatic venous effluent, and (3) denervation.

Each of these anatomic effects has been investigated as a possible contributor to alterations in glucose metabolism after pancreas transplantation.[3-5] We documented changes in glucose metabolism after pancreatic autotransplantation in which pancreatic ductal drainage is intraperitoneal. This circumstance is associated with marked exocrine atrophy and, perhaps, chronic pancreatitis.[4,5] Sollinger[6] and others[7,8] introduced an important technique in pancreas transplantation, using exocrine duct drainage into the urinary bladder. The advantage of this technique appears to be markedly decreased mortality and morbidity rates in clinical and animal models, but its effect on postoperative glucose metabolism has not been documented.

We sought to evaluate the effect of this important technique on glucose metabolism and compare it to a technique widely used in canine freely drained intraperitoneal segmental pancreas transplantation, which has been used as a model for human transplantation. This is an important consideration because many studies using the canine model have used the intraperitoneal technique because of its simplicity and the fact that it is well tolerated by the animals. We hypothesized that the bladder-drained technique might result in improvement in glucose metabolism, thereby increasing its attraction as an important technique for clinical pancreas transplantation. Therefore the bladder-drained animal model would be more appropriate to evaluate carbohydrate metabolism after pancreatic transplantation.

### Materials and Methods

All experiments were begun by 8:30 A.M. on overnight fasted, conscious female mongrel dogs (body weight, 20 to 24 kg) who had been trained to stand quietly in harnesses. The animals were kept on a weight-maintaining diet (Pro Pet dog food, Newark, DE) with exocrine pan-

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creatic supplement (10 g/day; Viokase, A.H. Robins, Richmond, VA). All provocative studies and surgical procedures were carried out in accordance with established federal and University of Virginia Vivarium guidelines (UVA protocol number 1126-06-85). At the time of study, each animal was clinically healthy and had maintained or regained its preoperative body weight. Four animals in each surgical group were allowed to recuperate from surgery for at least 6 weeks and then studied at least in duplicate.

### *Provocative Studies*

Oral glucose tolerance tests (OGTT) were performed on each animal. A bolus of 20% glucose (2 g/kg body weight; Travenol, Deerfield IL) was ingested by each animal within 5 to 10 minutes of delivery. A 16-gauge intravenous saphenous vein catheter was used for sample collections. After two separate basal samples were taken for measurement of glucose and insulin, sequential samples were drawn at 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes. Serum glucose values were determined immediately by the glucose oxidase method on the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). The remainder was separated into prechilled test tubes for subsequent insulin assay. All determinations were performed in duplicate. Plasma insulin levels were determined with a double-antibody radioimmunoassay by the University of Virginia Diabetes Core Laboratory.

For the hyperglycemic clamp studies, two 16-gauge catheters were placed in the saphenous vein of each hind limb. A central line was advanced 30 cm for glucose infusion. Sample collections were obtained from the peripheral line, eliminating any possibility of mixing. Fifteen minutes after catheter insertion, basal samples were obtained, after which a square wave of hyperglycemia (150 mg/dL above basal) was created rapidly and maintained for 120 minutes.[7,8] This was accomplished by a priming infusion of glucose followed by a computer-adjusted variable infusion of 20% glucose solution. The infusion rate adjustments were based on 5-minute plasma glucose determinations fed into a servo-controlled negative feedback formula coupled to a variable-speed infusion pump (Harvard Apparatus, Natick, MA). Samples were obtained every 5 minutes for determination of plasma glucose levels and every 10 minutes for determination of insulin levels.

### *Surgical Procedures*

*Pancreas autotransplant—intraperitoneal drainage (Fig. 1).* Female mongrel dogs were prepared for operation with overnight fasting. Each animal was anesthetized with sodium pentobarbitol (25 to 30 mg/kg), intubated with an endotracheal tube, placed on a volume respirator, and

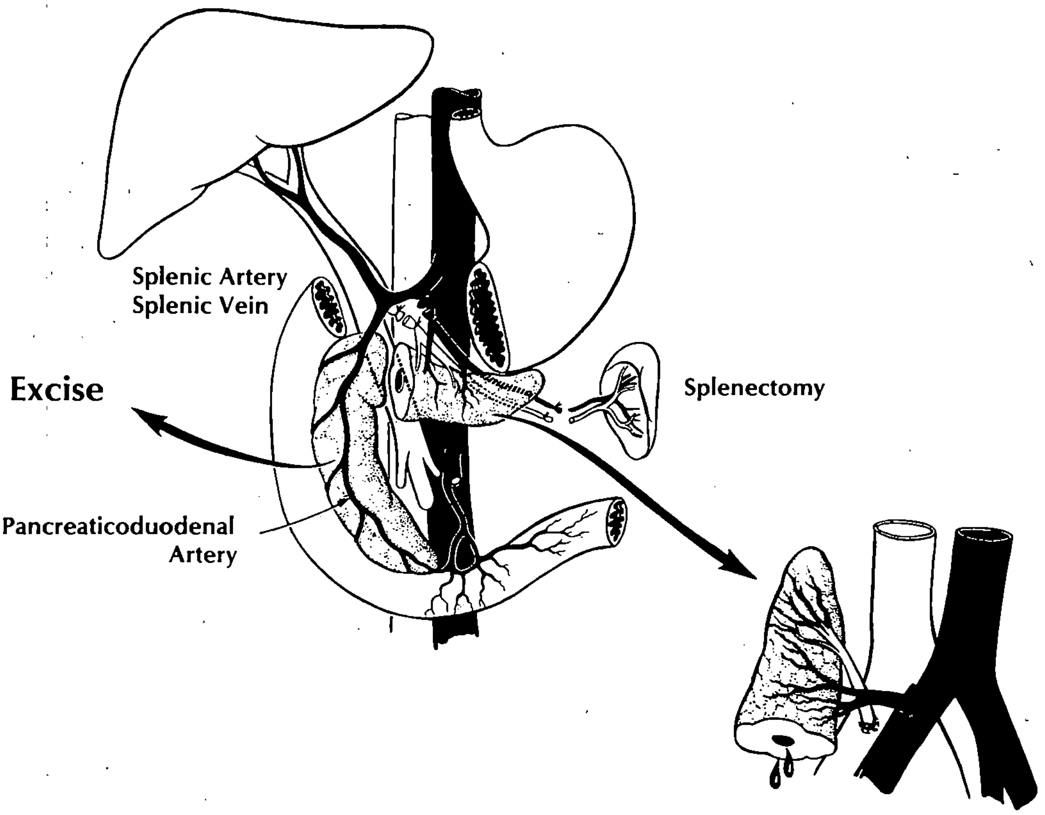

FIG. 1. The technique of intraperitoneal drainage (PAT). The details of the surgical procedure are outlined in the text.

given halothane anesthesia (2%). The abdomen was entered through a midline incision. Proximal pancreatectomy was performed, removing the duodenal lobe of the pancreas, preserving the vascular supply to the intact duodenum and leaving the splenic lobe of the pancreas intact. The splenic artery was identified as it left the celiac axis. The splenic vein was likewise identified. Hypothermic preservation by perfusion of chilled normal saline (containing 500 units heparin per liter) was performed in a retrograde fashion by cannulating the distal splenic artery using an 18-gauge catheter. The venous anastomosis then was accomplished in an end-to-side fashion into the iliac vein. An end-to-side arterial anastomosis was completed between the splenic and the external iliac artery. The pancreatic duct was allowed to drain into the abdominal cavity. We reported long-term survival of these animals, documenting clinical health, normal eating patterns, and return to preoperative body weight.[4,5] Postoperative animals received pancreatic exocrine supplementation as mentioned above.

*Pancreas autotransplant—urinary bladder drainage (PAT/B) (Fig. 2).* Laparotomy, proximal pancreatectomy, and autotransplantation of the splenic lobe were performed in an identical fashion as the PAT animals, as described above. On completion of this part of the procedure, an incision of approximately 1 cm in length was made in the external muscle layer of the bladder and carried to the mucosa. A 2-mm incision then was made in the bladder mucosa and this was reapproximated using interrupted sutures (6-0 absorbable) to the pancreatic duct over an 18-gauge polyethylene stent (2 cm long). The pancreatic capsule anteriorly and posteriorly was then approximated to the incised edge of the bladder musculature with 5-0 nonabsorbable sutures.

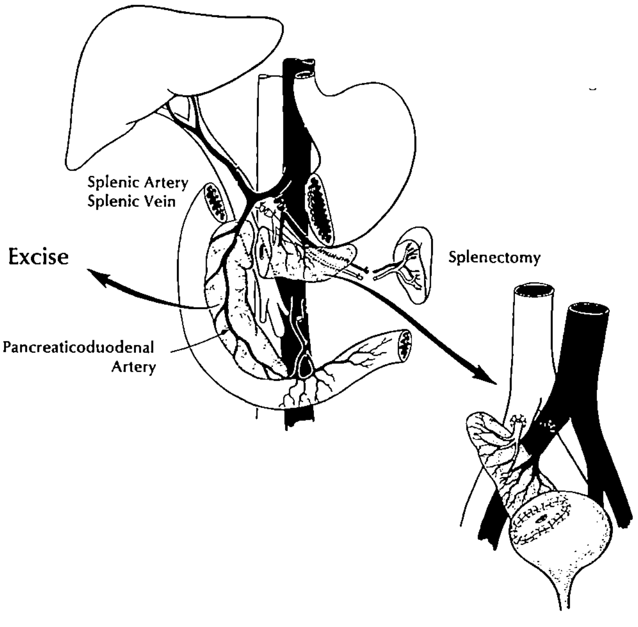

FIG. 2. The technique of urinary-bladder drainage (PAT/B). The details of the surgical procedure are outlined in the text.

### *Calculation and Statistical Analysis*

The mean concentrations of glucose and insulin were calculated for each time point for both clamp and oral challenge studies according to treatment protocol. Basal adjusted integrated responses for the oral glucose tolerance test were calculated by the trapezoidal rule. The integrated response then was divided by its time interval, resulting in a mean time-independent concentration. For clamp studies means of individual values were calculated for glucose, insulin, and the estimation of glucose metabolized (M = mg/kg/min) according to treatment. During hyperglycemia, M approximates the glucose infusion necessary to maintain the hyperglycemic plateau after corrections are made for volumes and kinetics of glucose distribution.[9,10] Mean values for the last 60-minute period of the clamp (60 to 120 minutes) then were analyzed. Means for all groups were simultaneously compared with each other using the general linear modeling analysis of variance, and significance was determined by the least squares means comparison method.[11]

## Results

Data for the oral glucose tolerance test, clamp studies, and basal values for glucose and insulin for the control and the two postoperative groups are presented in Table 1 and Figures 3 and 4.

### *Basal Values*

Basal (fasting) values for glucose and insulin in the three groups are presented in Table 1. The normal control value for glucose of 92 ± 4 mg/dL is not statistically different from either of the two postoperative groups. Normal insulin values of 12 ± 2 μU/mL are not statistically different than the PAT animals. The PAT/B animals had a fasting hyperinsulinemia of 22 ± 2 μU/mL.

### *Oral Glucose Challenge (OGTT)*

These data are presented in Figure 3 and Table 1. Pancreas autotransplantation animals have a statistically elevated integrated glucose response compared to normal controls (215 ± 12 mg/dL compared to 103 ± 11 mg/dL, respectively). The technique of bladder drainage results in a decrement in the integrated glucose response that is statistically less than PAT animals but still increased from normal controls. Interestingly the integrated insulin response after PAT is elevated. In Figure 3 this is apparent

TABLE 1. *Insulin Response to Oral (OGTT) and Intravenous Hyperglycemic (Clamp) Challenge*

| | Basal | | OGTT | | Clamp (60–120 min) | | | |
|---|---|---|---|---|---|---|---|---|
| | G | INS | G INT | INS INT | G | INS | M | M/INS |
| Control | 92 ± 4 | 12 ± 2 | 103 ± 11 | 32 ± 5 | 240 ± 3 | 74 ± 7 | 26 ± 2 | .38 ± .1 |
| PAT | 96 ± 3 | 16 ± 3 | 215 ± 12* | 50 ± 6* | 244 ± 3 | 54 ± 7* | 16 ± 2* | .35 ± .1 |
| PAT/B | 99 ± 2 | 22 ± 2† | 138 ± 6†‡ | 36 ± 3 | 253 ± 4 | 83 ± 8‡ | 18 ± 2† | .20 ± .1 |

* Control *vs.* PAT ($p < 0.05$).
† Control *vs.* PAT/B ($p < 0.05$).
‡ PAT *vs.* PAT/B ($p < 0.05$).
n = 8.

G, glucose (mg/dL); INS, insulin (μU/mL); M, glucose metabolized (mg/kg.min-1); PAT, intraperitoneal duct drainage pancreas autotransplant; PAT/B, bladder-drained pancreas autotransplant; G INT, integrated glucose response; INS INT, integrated insulin response.

by a delayed peak and elevated insulin values from the 90-minute to 240-minute time period. The technique of bladder drainage results in an insulin response that more closely recapitulates normal with peak values at 30 minutes and with an integrated response not statistically different from control (36 ± 3 μU/mL compared to 32 ± 5 μU/mL).

### *Hyperglycemic Clamp Challenge*

These data are presented in Table 1 and Figure 4. All three groups were clamped for a 2-hour period in statistically equivalent hyperglycemic ranges. The insulin response by the normal animals can be seen as abrupt response to hyperglycemia in the 50 to 60 μU/mL range, which increases during the clamp to 74 ± 7 μU/mL during the last 60 minutes. Pancreas autotransplantation animals have an abrupt elevation to levels equivalent to control during the first hour (Fig. 4). Pancreas autotransplantation animals, however, are unable to elevate peripheral insulin levels in response to hyperglycemia and, by the 60-to-120-minute period of the clamp, have an average peripheral insulin level of 54 ± 7 μU/mL, which is statistically lower than control values. Pancreas autotransplantation urinary bladder animals have a hyperinsulinemic response compared to controls with levels immediately approaching 80 to 90 μU/mL. By the 60-to-120-minute interval, they remain statistically equivalent to control animals and significantly elevated compared to PAT.

M values are presented in Table 1 and Figure 4. In control animals the M value elevation during the hyperglycemic challenge reflects endogenous insulin levels. M values increase from approximately 20 mg/kg/min at the beginning of the clamp to reach 26 ± 2 mg/kg/min by the last 60 minutes of the clamp. Both surgical groups have statistically decreased M values over the period of the clamp. Pancreas autotransplantation and PAT/B (16 ± 2, 18 ± 2 mg/kg/min, respectively) remain significantly depressed compared to control animals, despite the obvious differences in endogenous insulin during the same interval. M/INS ratios for controls, PAT, PAT/B are 0.38 ± 0.1, 0.35 ± 0.1, and 0.20 ± 0.1, respectively.

## Discussion

Clinical pancreas allotransplantation is enjoying nearly exponential growth worldwide in the last decade. As the understanding for its applicability has become more apparent, increasing questions arise concerning postoperative alterations in carbohydrate metabolism. The recognized surgical alterations that might affect postoperative function of the endocrine pancreas have been studied to delineate which of several might impact on glucoregulation after transplantation. The most important of these surgical alterations are (1) reduction in beta cell mass, (2) systemic drainage of pancreatic venous insulin, and (3) denervation.

Reduction of beta cell mass could be predicted to have definite impact on peripheral insulin levels. Previously we reported decreased insulin levels after intravenous oral challenge using an 80% pancreas resection model and we concur with the findings of others that this results in similar alterations in carbohydrate metabolism.[3,4] Bonner-Weir[12] and Leahy[13] used a surgically reduced beta cell mass in a rat model and hypothesized that this reduction leads to selective loss of glucose-induced insulin secretion. Marincola[14] studied dogs with an 80% pancreatectomy model and hypothesized that an accommodation to severe islet reduction occurs by important extrapancreatic mechanisms, suggesting alterations in peripheral sensitivity to the reduced insulin load.

Previously we reported that insulin levels in PAT animals are statistically increased from partial pancreatectomy animals (equivalent reduced beta cell mass but with portal venous drainage intact), which suggests that the systemic release of insulin is important in elevation of these insulin values.[5] Probably this is due to bypassing 'first pass' hepatic extraction of insulin, which has been shown to range between 40% and 60% in fasting dogs.[15] Interestingly, however, the alterations in glucose response to orally administered glucose in these PAT animals are not corrected by these 'normal' insulin values. These data suggest that perhaps 'insensitivity' exists to the endogenously released insulin, which is systemically released after pancreas transplantation. Analyzing the clamp data (Table

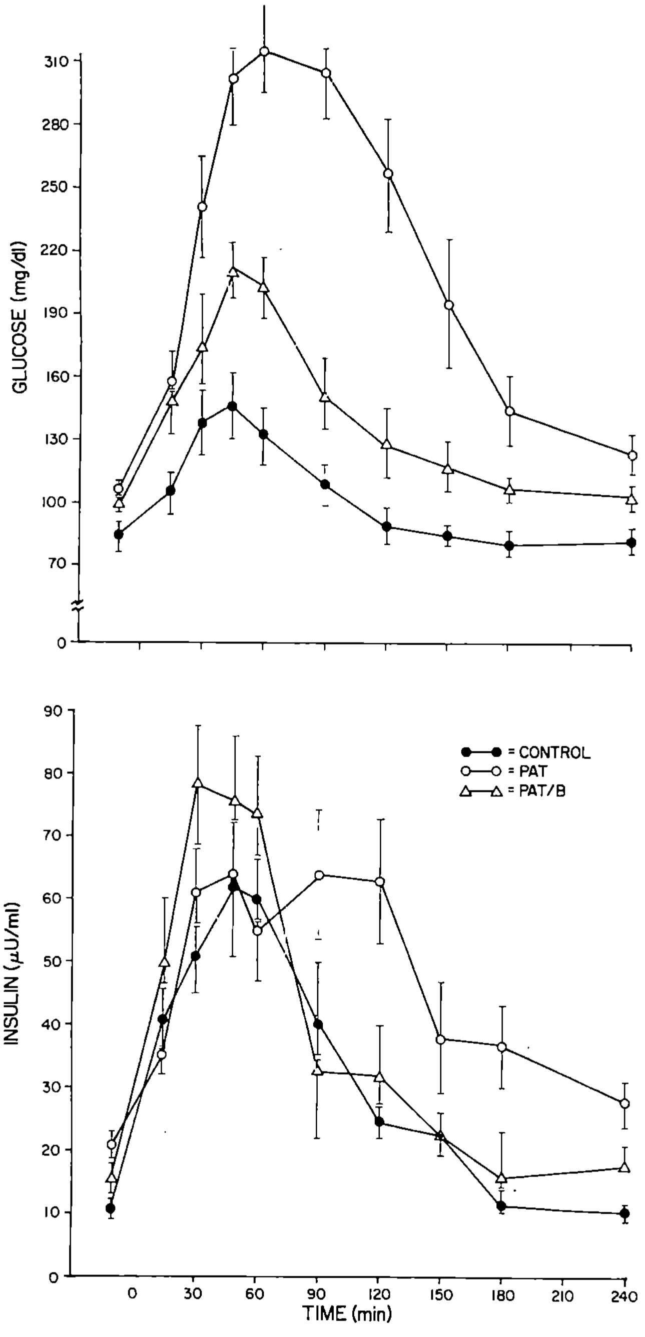

FIG. 3. Oral glucose challenge (OGC). The data for the OGTT are discussed in the text and in Table 1.

1 and Fig. 4) and the OGTT data (Table 1 and Fig. 3) demonstrate these effects. The oral glucose challenge restores peripheral levels of insulin comparable to normal controls, yet the integrated glucose response remains significantly altered. We documented these effects in earlier studies.[4,5] These results correlate with others that demonstrate that systemic drainage is effective in normalizing peripheral insulin levels; however the concomitant effect on glucose metabolism is unclear.[16]

A great deal of literature exists as to the appropriate handling of exocrine pancreatic secretion after pancreas transplantation. The human body clearly does not tolerate a freely drained intraperitoneal duct whereas the canine body can. We have reported severe histologic changes resulting in loss of identifiable exocrine structures after this technique.[4] The intraperitoneal drainage technique or duct ligation is probably associated with a model of pan-

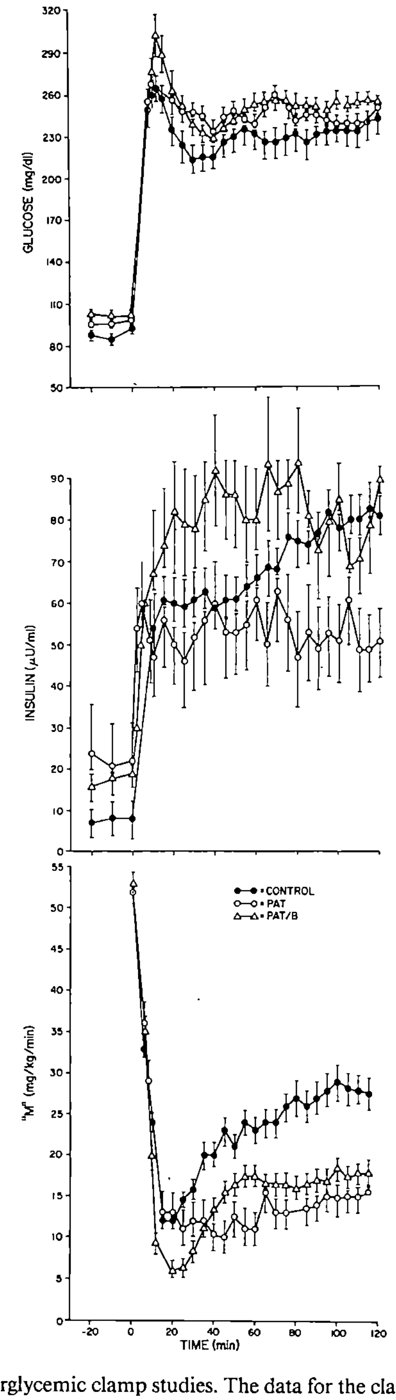

FIG. 4. Hyperglycemic clamp studies. The data for the clamp studies are discussed in the text and in Table 1.

creatitis in the dog that markedly impairs peripheral glucose levels and patterns of insulin secretion after either intravenous or oral glucose challenge.[5,17] In addition others have reported studies using polymer injection techniques, enteric drainage techniques, as well as urinary (ureter and bladder) drainage techniques. The apparent common denominator in all of these techniques is the desire to control digestive enzymes that might disrupt enteric anastomoses or, in addition, be associated with graft pancreatitis. Graft pancreatitis has been hypothesized to alter insulin secretion and consequent carbohydrate metabolism.[18–20] The urinary bladder technique obviates the need for enterotomy and has been associated with increasing clinical success. In addition monitoring of urinary amylase permits early diagnosis of rejection before any alteration in peripheral glucose levels.

In the present study, a distinct difference in insulin secretory patterns was identified comparing the two techniques of exocrine pancreatic drainage. The oral glucose challenge resulted in a distinctly different insulin response for PAT animals compared to PAT/B animals. Despite the fact that the integrated insulin response was less than for the PAT animals, the timing of the initial insulin peak is associated with a decline in the integrated glucose response that approximated the control values. Comparing the results of the two surgical techniques suggests that the initial endogenous insulin peak is an important phenomenon in peripheral glucose disappearance rather than the integrated insulin response *per se.*

The clamp data also are interesting. An entirely different insulin response is demonstrated after the technique of bladder drainage. The PAT animals failed to elevate insulin and have a significantly blunted response, as shown by the peripheral levels in the last 60 minutes of the clamp. The PAT/B animals demonstrate an initial exaggerated insulin response to intravenous challenge that matches the control response by the last hour of glucose infusion. Interestingly, however, both surgical groups have decreased M values that confirm our previous observations about the possibility of insensitivity to these endogenous levels. M/INS ratios demonstrate a decrease from 0.38 ± 0.1 for controls to 0.20 ± 0.1 for the PAT/B animals. Therefore these data suggest a possibility of peripheral insensitivity to the endogenous insulin of the PAT/B animals, but further studies would be needed for absolute confirmation. These data appear to correlate with Marincola's data that extrapancreatic mechanisms may be operative after pancreatic transplantation.[14] This finding might be explained more completely by evaluating peripheral insulin receptor status.

The explanation for these effects is unclear. There is an obvious, complex interplay of anatomic and physiologic changes that occurs after transplantation. We used the autotransplant model (devoid of immunosuppression) to try to evaluate these. The two surgical models share in common the three anatomic changes that previously we documented to have important consequences on postoperative metabolism, beta cell reduction, denervation, and systemic drainage of insulin. The only difference between the two groups is the urinary bladder drainage of the exocrine pancreatic duct. In our experience, the latter technique has been associated with increased animal survival (approaching 80% as opposed to approximately 50% previously), and an obvious grossly different pancreatic morphology. The bladder-drained animals have a normal pancreatic remnant identifiable for as long as 3 months after operation. Clearly further histologic and morphologic studies will be needed to confirm this preliminary finding.

One can hypothesize that the important changes that are associated with pancreatitis are minimized by the bladder drainage technique and, therefore, result in significant increases in peripheral insulin levels. The interesting aspect of these observations is the fact that the peripheral levels of insulin *per se* do not correct completely the alterations of carbohydrate metabolism. For example the increased basal insulin levels seen after PAT/B are associated with equivalent glucose levels, suggesting a possible insensitivity in the basal state to increased levels of insulin. In addition increased insulin levels in response to the clamp studies after the PAT/B technique do not result in an amelioration of the M values, again suggesting that glucose insensitivity in the periphery may occur. This unique finding allows a dose-response observation of endogenous insulin levels using the different techniques to demonstrate that postoperative alterations in carbohydrate metabolism may exist independent of the endogenous levels of insulin. The contributions of hepatic glucose output and more complete studies on peripheral sensitivity using exogenous insulin infusions may well be necessary to clarify these observations.

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## References

1. Sutherland DER, Goetz FC, Najarian JS. One hundred pancreas transplants at a single institution. Ann Surg 1984; 200:414–440.
2. Sutherland DER, Dunn DL, Goetz FC, et al. A 10-year experience with 290 pancreas transplants at a single institution. Ann Surg 1989; 210:274–288.
3. Florack G, Sutherland DER, Squifflet JP, et al. Effect of graft denervation, systemic venous drainage and reduction of beta cell mass on insulin levels after heterotopic pancreas transplantation in dogs. Surg Forum 1982; 33:351.
4. Calhoun P, Brown KB, Krusch DA, et al. Evaluation of insulin secretion after pancreas autotransplantation by oral or intravenous glucose challenge. Ann Surg 1986; 204:585.

5. Krusch DA, Brown KB, Calhoun P, et al. Peripheral insulin levels after pancreatic autotransplantation: the effect of reduction of beta cell mass with or without systemic drainage. Endocrinology 1988; 123:426.
6. Sollinger HW, Cook K, Kamps D, et al. Clinical and experimental experience with pancreaticocystostomy for exocrine pancreas drainage in pancreas transplantation. Transplant Proc 1984; 16: 749–751.
7. Prieto M, Sutherland DER, Goetz FC, et al. Pancreas transplant results according to technique of duct management: bladder vs enteric drainage. Surgery 1987; 102:680–691.
8. Munda R, First MR, Webb CB, et al. Clinical experience with segmental pancreatic allografts. Transplant Proc 1984; 16:692.
9. Andres R, Swerdloff RS, Pozefsky T, Coleman D. Manual feedback technique for the control of blood glucose concentration. *In* Skeggs LT, ed. Automation in Analytical Chemistry (Technicon Symposium). New York: Mediad, 1966; pp 486–491.
10. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979; 237(Suppl):214–223.
11. Goodnight JG, Harvey WR. Least square means in the fixed effects general linear model. *In* SAS Technical Report R-103. Raleigh, NC:SAS Institute, 1978; pp 18–23.
12. Bonner-Weir S, Trent DF, Weir GC. Partial pancreatectomy in the rat and subsequent defect in glucose-induced insulin release. J Clin Invest 1983; 71:1544–1553.
13. Leahy JL, Bonner-Weir S, Weir GC. Abnormal glucose regulation of insulin secretion in models of reduced B-cell mass. Diabetes 1984; 33:667–673.
14. Marincola F, Cobb LF, Horaguchi A, et al. Accommodation to a reduced islet cell mass in dogs. Am J Physiol 1984; 247:E456–E461.
15. Hanks JB, Andersen DK, Wise JE, et al. The hepatic extraction of gastric inhibiting polypeptic (GIP) and insulin. Endocrinology 1984; 115–1011.
16. Baumgartner D, Illig R, Sutherland DER. Effect of venous drainage to the vena cava and denervation on endocrine function of pancreatic segments in dogs. Transplant Proc 1984; 16:769–772.
17. Yeo CJ, Bastidas JA, Schmieg RE, et al. Pancreatic structure and glucose tolerance in a longitudinal study of experimental pancreatitis-induced diabetes. Ann Surg 1989; 210:150–158.
18. Gooszen HG, Schilfgaarde RV, Frolich M, Van Der Burg MPM. The effects of duct obliteration and of autotransplantation on the endocrine function of canine pancreatic segments. Diabetes 1985; 34:1008–1013.
19. Van Der Burg MPM, Gooszen HG, Guicherit OR, et al. Contribution of partial pancreatectomy, systemic hormone delivery, and duct obliteration to glucose regulation in canine pancreas. Importance in pancreas transplantation. Diabetes 1989; 38:1082–1089.
20. Cutfield RG, Polonsky K, Olson L, et al. Long-term follow-up of canine segmental pancreatic autografts. Diabetes 1985; 34:174–178.

# Diets Enriched with N-3 Fatty Acids Ameliorate Lactic Acidosis by Improving Endotoxin-induced Tissue Hypoperfusion in Guinea Pigs

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**The effect of 6 weeks dietary lipid manipulation on the acute physiologic response to 7-hour continuous endotoxin infusion in guinea pigs was examined. One diet was enriched with N-3 fatty acids, whereas the other contained N-6 fatty acids, primarily linoleic acid. Animals fed N-6 fatty acids developed significant lactic acidemia, microvascular muscle hypoperfusion, and pulmonary infiltrates in response to endotoxin infusion. N-3 fatty acid-fed animals demonstrated improved lactate levels, microvascular muscle perfusion, and lung morphology compared to N-6 fatty acid-fed animals after endotoxin infusion. There was no significant change in cardiac output, $PaO_2$, or mean arterial blood pressure at the end of the endotoxin infusion in either group. Pretreatment with indomethacin, or BM 13505, a specific thromboxane $A_2$ receptor blocker, ameliorated the development of metabolic acidosis in N-6 fatty acid-fed animals, demonstrating a role for prostanoids in the sequelae of endotoxemia. The ability of dietary pretreatment with N-3 fatty acids to influence favorably the physiologic response to endotoxin represents a novel nutrient–metabolic interaction with potential therapeutic implications.**

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ENDOTOXIN SHOCK IS a highly complex pathophysiologic phenomenon that occurs when there is release of endotoxin from gram-negative organisms[1] or when endotoxin is administered experimentally.[2,3] Endotoxins are lipopolysaccharide protein lipid complexes that are released from the cell membrane of killed bacteria. Endotoxemia can result in septic shock, which is often lethal to most patients who are affected.[4] Although the exact mechanism of endotoxin shock is not known, endogenous cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF) are released after endotoxin administration, and in animals have reproduced many features of septic shock.[5,6]

Substantial evidence has accumulated to suggest that arachidonic acid metabolites may be a common efferent signal in the pathogenesis of septic shock.[7–12] Plasma levels of prostaglandin $E_2$, prostacyclin $I_2$, and thromboxane $A_2$ all are increased during endotoxemia and after cytokine administration.[8,9] Thromboxane may be an especially important mediator because thromboxane antagonism prevented ischemia-induced neutrophil oxidative burst in rats[10] and improved $O_2$ delivery and $O_2$ consumption in burned sheep.[11] In further support of this postulate, rats made essentially fatty acid deficient (leading to decreased arachidonic acid concentration in tissue phospholipids) demonstrated significantly improved survival from endotoxemia compared to controls and failed to show any endotoxin-induced elevation of thromboxane $A_2$.[12]

Although several investigators demonstrated the benefit of pharmacologic inhibition of prostaglandin metabolytes in the amelioration of septic shock, results to date have not been uniform.[13] Cyclo-oxygenase or thromboxane synthetase inhibitors can redirect the metabolism of arachidonic acid toward production of other intermediary eicosanoids.[14–16] Aspirin can increase the formation of 5-lipoxygenase products and thromboxane synthetase inhibitors divert the metabolism of arachidonic acid to form cyclic endoperoxides, which serve as physiologic agonists.[17] The biologic effects of the endoperoxides are not well understood and may explain the conflicting reports about the efficacy of nonsteroidal anti-inflammatory agents in shock.

Recent studies attempting to elucidate the physiologic effects of diets rich in N-3 fatty acids have centered on the alterated formation and metabolism of prostanoids.[18–22] Eicosapentaenoic acid (EPA, 20:5,N-3) has been shown to be the metabolically active fatty acid in fish oil because of its structural similarity to the usual prostaglandin precursor, arachidonic acid (AA, 20:4,N-6). Arachidonic acid is derived from the N-6 family of fatty acids and gives rise to the dienoic or '2' series of prostaglandins and the '4' series of leukotrienes. Eicosapentaenoic acid is derived

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from the N-3 family of fatty acids and forms the trienoic or '3' series of prostaglandins and the '5' series of leukotrienes.[23]

The biologic activities of these two families of prostaglandins and leukotrienes differ significantly. Thromboxane $A_2$, synthesized by platelets from arachidonic acid, is a very potent platelet aggregator and vasoconstrictor.[24] Thromboxane $A_3$, formed from EPA, is a moderate vasoconstrictor but will not aggregate platelets.[25,26] Leukotriene $B_4$, made from arachidonic acid, is a potent chemotactic and aggregatory agent for neutrophils.[27] Leukotriene $B_5$ derived from EPA is 12% as chemotactic and 5% as active as an aggregating agent relative to leukotriene $B_4$ derived from arachidonic acid.[27] However prostacyclin $I_2$ synthesized in endothelial cells from arachidonic acid and prostacyclin $I_3$ derived from EPA are potent vasodilators and platelet antiaggregators.[28] Thus controlled dietary intake of select fats rich in EPA and N-3 fatty acids can significantly down regulate eicosanoid metabolism leading to a more vasodilatory, platelet, and neutrophil antiaggregatory state relative to diets enriched with N-6 fatty acids.

Previously we demonstrated that dietary pretreatment with N-3 fatty acids for 6 weeks attenuated the febrile response, reduced thromboxane formation to exogenous IL-1 administration, and improved survival to endotoxin challenge in guinea pigs.[9,29] The mechanism(s) for the latter observation have not been elucidated yet. Our hypothesis was that manipulation of membrane phospholipid with diets enriched with N-3 fatty acids may alter the physiologic response to endotoxin. We present evidence that dietary pretreatment with N-3 fatty acids effectively ameliorate the development of metabolic lactic acidosis in guinea pigs by improving endotoxin-induced tissue hypoperfusion through a prostaglandin-dependent mechanism.

## Methods

### *Animal Feeding and Catheterization*

All animal protocols first were approved by the New England Deaconess Hospital Animal Care and Usage Committee. Male Hartley guinea pigs (200 to 250 g body weight; Elm Hill Breeding Lab., Chelmsford, MA) were housed individually in plastic cages with pine shavings in a light- and temperature-controlled room. The animals were randomized into two groups to be group fed a modified Reid-Briggs guinea pig diet (Table 1) containing either menhaden oil (14.5% w/w diet) or safflower oil (15% w/w diet) for 6 weeks. One half per cent by weight of safflower oil (0.5% w/w diet) was added to the fish oil diet to prevent essential fatty acid deficiency. Body weights were recorded tri-weekly to ensure similar weight gain in both groups.

TABLE 1. *Composition of Reid-Briggs Guinea Pig Diet (Modified)*

| Ingredient | g/kg |
|---|---|
| Casein | 300 |
| Corn starch | 190 |
| Sucrose | 102 |
| Cellulose | 150 |
| *Lipid | 150 |
| Salt mix 200151 | 90 |
| Vitamin mix 300151 | 10 |
| Choline chloride | 8 |

Diets were prepared commercially and refrigerated to ensure freshness (Dyets Inc., Bethlehem, PA). Lipid was stabilized with 0.2% TBHQ.

* Lipid consisted of either safflower oil or menhaden fish oil. Animals were pair-fed to ensure similar food intake. Composition of the standard salt and vitamin mix is available from Dyets Inc. Choline chloride content was increased proportionally with the increased lipid content compared to standard Reid-Briggs diet that contained 7.3% lipid (Reid ME, Briggs J . J Nutr 1953; 51:341).

TBHQ, Tert-Butylhydroquinone.

After the 6-week feeding period, all animals were anesthetized (Ketamine HCL, 125 mg/kg administered intramuscularly) and underwent right internal jugular vein and left carotid artery catheterization under sterile conditions. A silastic catheter (0.025″ inner diameter [id] × 0.047″ outer diameter [od]) was placed in the jugular vein for endotoxin infusion, and a polyethylene catheter (PE 10, 0.011″ id × 0.024″od) was placed in the left carotid artery for arterial blood sampling. For experiment 2, a second arterial catheter was placed in the right carotid artery and advanced to the left ventricle. The catheters were externalized in the midscapular region and attached to a flow-through swivel to permit free movement of the animals. The arterial catheters were kept patent by a heparin lock. The venous catheter was kept patent by a saline infusion (1 mL/hr) that also served to resuscitate the animals after surgery. The animals were allowed to recover overnight in individual cages before experimentation.

### *Experimental Protocols*

*Experimental design.* Three experiments were conducted to determine the influence of N-3 fatty acid feeding and/or prostanoid antagonism on altering the physiologic response to endotoxin. In the first experiment, blood pH, $paCO_2$, $paO_2$, $HCO_3$, and pressure were monitored hourly in animals continuously infused with endotoxin during a 7-hour period. In addition plasma lactate, serum phospholipid fatty acid profiles, and histology of lung, liver, and kidney were determined at the end of the study. The 7-hour time period was selected to study the acute changes during endotoxemia because previous survival studies in our laboratory, with similarly treated animals given the same dose of endotoxin, demonstrated that most of the animal deaths occurred within the first 8 to 15 hours of endotoxemia.[24]

In the second set of experiments, the influence of dietary lipid manipulation on cardiac output and blood flow distribution during endotoxemia were determined. These determinations were made in conscious guinea pigs using radiolabeled microspheres.

During the third set of experiments, the effect of indomethacin, or a specific thromboxane $A_2$ receptor blocker (BM 13505; 4-2-lorobenzenesulphonylamino]-ethyl benzene acetic acid, provided by Dr. H. Patscheke, Boehringer Mannheim GmbH, Mannheim, FRG) on altering the response to endotoxemia was examined in animals fed safflower or menhaden oil. This study served to determine the relative importance of arachidonic acid metabolites and thromboxane in the sequelae of endotoxemia. Finally an additional subset of animals were infused with 300 mg/kg/hr of dichloroacetic acid (DCA). Dichloroacetic acid prevents inhibition of the pyruvate dehydrogenase enzyme complex (PDH) by endotoxin. This study was conducted in an attempt to potentiate the lactate-lowering effect of N-3 fatty acid feeding during endotoxemia.[30]

*Experiment 1.* On the morning of the study at approximately 6 A.M., animals fed menhaden (n = 20) or safflower oil (n = 20) diets for 6 weeks were placed in metabolic cages and further randomized to receive a 7-hour saline infusion (1.2 mL/hr) or saline-containing endotoxin infusion (LPS, *Escherichia Coli* 026:B6, Difco Inc., Detroit, MI) at a dose of 0.5 mg/kg/hr. Baseline arterial blood pH, $paCO_2$, $paO_2$, $HCO_3$, and pressure were recorded 1 hour before experimentation. Blood pH, $paCO_2$, $paO_2$, $HCO_3$, and pressure then were monitored hourly using a semiautomated blood gas analyzer (Corning Model 168, Corning Medical, Medifield, MA) and pressure transducer (Model P23, Gould Inc., Oxnard, CA) interfaced with a multichannel polygraph (Grass Inc., Quincy, MA). The alveolar to arterial gradient (A-a) was calculated hourly using standard formulas. Both blood gas analyzer and pressure transducer were calibrated hourly before each series of measurements. At the end of the study, animals were exsanguinated for determination of plasma lactate concentration and phospholipid fatty acid profiles. Tissue samples of lung, liver, and kidney were placed in buffered (pH 7.4) 10% formalin for histologic examination. Lung tissue was obtained after inflating the lungs with 15 mL of buffered formalin *via* a catheter placed in the trachea. All tissue samples were processed and stained with hematoxylin and eosin for light microscopy. Duplicate samples were fibrin stained for screening of microemboli in the tissues. Prepared slides were examined by a resident pathologist at the New England Deaconess Hospital and an attending pathologist at the Mallory Institute of Pathology, Boston, Massachusetts who did not know the diet or treatment given to each animal.

Plasma lactates were determined enzymatically at 340 nm by monitoring the reduction of $NAD^+$ (Boehringer Mannheim Biochemicals, Indianapolis, IN). Fatty acid profiles were determined by gas chromatography after the phospholipid fraction was extracted from the plasma using chloroform and methanol and separated from other fractions using thin-layer chromatography. The phospholipid fatty acids then were converted to methyl esters of fatty acids by using boron triflouride in methanol as a transesterification catalyst. Fatty acid methyl esters were separated and measured on a gas chromatograph (Sigma 2000, Perkin Elmer, Norwalk, CT) using a 50-m fused silica capillary column (Supelco, Bellefonte, PA). Helium was used as the carrier gas with the oven temperature programmed to hold at 190 C for 10 minutes and then increase 2 C per minute to a final temperature of 220 C. Detector and injector temperatures were 240 C. Methyl esters were identified by comparison with relative retention times of authentic standard mixtures (NuChek, Elysian, MN).

*Experiment 2.* This experiment was designed to measure changes in cardiac output and blood flow distribution associated with endotoxin infusion using radioactive $^{85}Sr$ microspheres (NEN-TRAC; 16.5 $\mu m \pm 0.1$ diameter, density $3.04 \times 10^5$ microspheres per mg, suspended in 10% dextran). Animals (n = 8 in each dietary group) were treated similarly as in the previous study, except an additional carotid catheter was placed and advanced into the left ventricle. Guinea pigs were allowed to recover overnight before experimentation. At the end of the endotoxin infusion period, a microsphere dose ranging between 500,000 and 1,000,000 $^{85}Sr$-microspheres suspended in 10% dextran with 0.01% Tween 80 was prepared for each guinea pig. Immediately before injection into the left ventricle, microspheres were sonicated in warm water for 20 minutes and vortexed repeatedly. An aliquot was taken for measurement of the syringe content and the microsphere dose was injected over 20 seconds. Two minutes later the animals were killed by an overdose of ketamine chloride. Tissues then were sampled, weighed, and counted in a gamma counter (Model 5500; Beckman Instruments) for $^{85}Sr$ content. Residual radioactivity remaining in the injection syringe and silastic tubing also was counted and subtracted from the total counts per syringe. In addition to this procedure, guinea pigs had their left carotid catheters attached to syringe withdrawal pumps (Harvard Instruments, S. Natick, MA), which were activated at a rate of 0.76 ± 0.03 mL/min beginning 10 seconds before the microsphere injection. Withdrawal of the reference blood continued for 2 minutes. Necropsy was performed to ensure proper catheter placement in the left ventricle.

*Experiment 3.* This experiment was conducted to determine if either indomethacin, BM 13505, a specific thromboxane receptor blocker, or dichloracetic acid infusion could reproduce the effects observed with N-3 fatty acid feeding alone. Animals (n = 8 in each group) were

TABLE 2. *Plasma Phospholipid Fatty Acid Profiles After Fish-oil or Safflower-oil Feeding*

| Fatty Acid | Fish Oil % | Safflower Oil % |
|---|---|---|
| 16:0 | 26.9 ± 0.8† | 16.3 ± 2.4 |
| 18:0 | 27.5 ± 0.6 | 23.1 ± 3.2 |
| 18:1, N-9 | 8.9 ± 0.2† | 4.4 ± 0.7 |
| 18:2, N-6 | 12.5 ± 1.3† | 39.8 ± 5.5 |
| 18:3, N-3 | 0.5 ± 0.2 | 0.1 ± 0.4 |
| 20:4, N-6 | 6.9 ± 0.4 | 5.2 ± 0.5 |
| 20:5, N-3 | 6.0 ± 1.1† | 0.0 ± 0.0 |
| 22:6, N-3 | 9.6 ± 0.4† | 0.6 ± 0.6 |
| Total N-3 fatty acids | 16.1 ± 1.7† | 0.7 ± 1.0 |
| Total N-6 fatty acids | 19.4 ± 1.7† | 47.0 ± 6.0 |

Plasma phospholipid fatty acid profiles were determined by gas chromotography after the plasma phospholipid fraction was extracted and separated by thin-layer chromatography. Results are expressed as percentage of total analyzed and are reported as mean ± SEM. Significance was determined by Scheffe's multiple comparison test after the overall analysis of variance was found to be significant, $p < 0.001$ by ANOVA; †$p < 0.01$ *vs.* safflower oil by Scheffe.

treated exactly as in experiment 1, except guinea pigs were randomized further to have either indomethacin (group 1, 5 mg/kg BW, Indocin ®, Merck Sharp & Dohme, West Point, PA), BM 13505 (group 2, 20 mg/kg BW), or dichloracetic acid (group 3, 300 mg/kg BW) added to the infusate. Arterial blood pH, $paCO_2$, $paO_2$, $HCO_3$, and lactate were determined as previously described.

### *Calculations*

*Tissue perfusion and blood flow.* Tissue perfusion (q), expressed as a fraction of the cardiac output, was calculated from the following relationship:

$$q = \frac{\text{tissue } ^{85}\text{Sr counts}}{\text{microsphere dose}} \qquad (1)$$

Estimates of cardiac output, in which a reference arterial sample was withdrawn at a constant rate, were made according to the following relationship[31,32]:

$$\frac{\text{CO}}{\text{microsphere dose}}$$

$$= \frac{\text{rate of withdrawal of reference blood}}{\text{activity in reference blood}} \qquad (2)$$

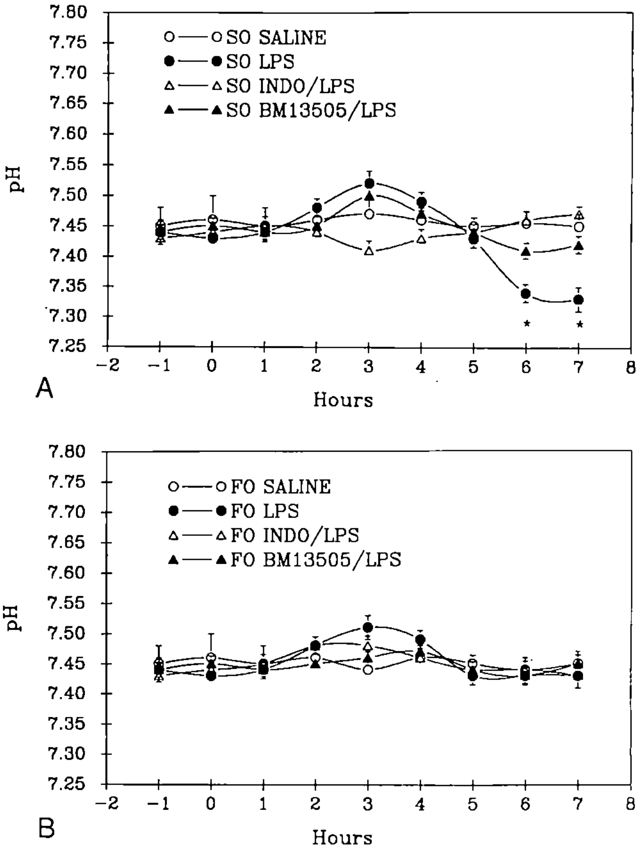
where CO is cardiac output, and microsphere dose is the total $^{85}$Sr counts of the injected microspheres. Calculation of actual tissue perfusion is the product of the cardiac output derived from equation 2 and percentage perfusion derived from equation 1 for each tissue studied.

*Statistical analysis.* Statistical significance was tested separately in each experiment by two-way analysis of variance (ANOVA) using a computer program statistical package (BMDP, Regents of the University of California). Intergroup comparisons were made with Student's t test and Scheffe's multiple comparison test when the overall ANOVA was significant ($p < 0.05$). Mortality was assessed using chi square analysis.

## Results

Neither initial body weights of animals receiving fish or safflower oil diets (224 ± 5.1 g *versus* 227 ± 4.8 g, respectively), nor change in body weight after 6 weeks of feeding (481.3 ± 7.2 g *versus* 490 ± 8.0 g, respectively) were statistically different.

The observed mortality rate in animals infused with endotoxin alone was 20% in safflower oil-fed animals and



FIGS. 1A to 4B. Arterial blood gas profiles after endotoxin infusion in guinea pigs fed fish or safflower oil for 6 weeks. A figures represent safflower oil-fed animals receiving the various infusion regimens, while B figures represent fish oil-fed animals receiving the same infusion regimens. SO SALINE = Safflower oil-fed and infused with saline; SO LPS = Safflower oil-fed and infused with endotoxin; SO INDO/LPS = Safflower oil-fed and infused with indomethacin and endotoxin. Indomethacin infusion was started 1 hour before endotoxin. SO BM 13505/LSP = Safflower oil-fed and infused with the thromboxane receptor blocker BM 13505 and endotoxin. BM 13505 infusion was started 1 hour before endotoxin infusion. FO SALINE; FO LPS; FO INDO/LPS; FO BM 13505/LPS; are equivalent to above except animals were fed fish oil rather than safflower oil 6 weeks before experimentation. Arterial blood pH, $pCO_2$, $pO_2$, and $HCO_3$ were determined hourly after baseline values were recorded. Blood samples (0.2 mL) were collected in heparinized syringes and analyzed immediately. Values are mean ± SEM. * = $p < 0.05$ *vs.* control by Scheffe's method after overall ANOVA was significant, $p < 0.05$.

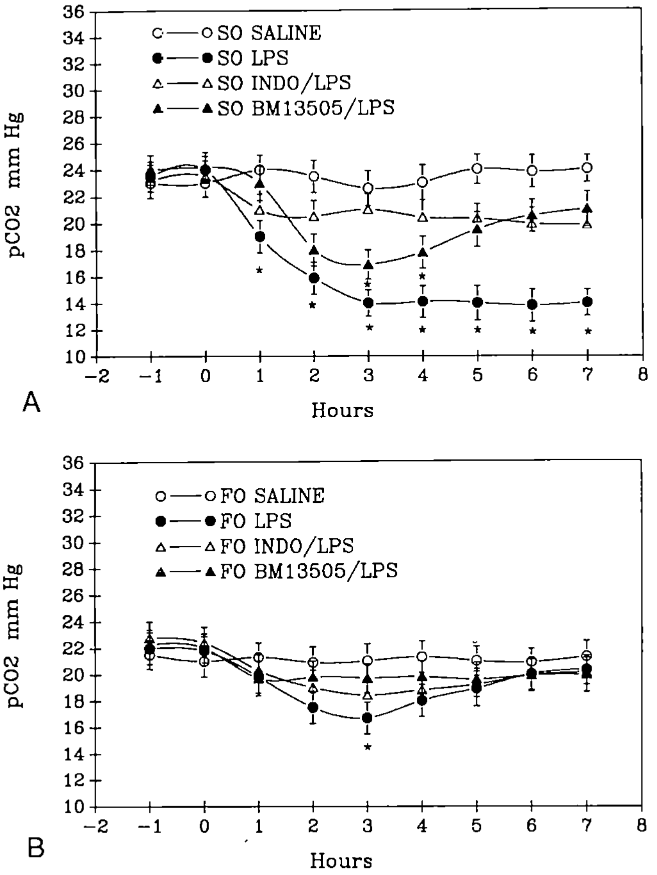


FIG. 2A and B. See legend to Figure 1 for explanation of abbreviations.

10% in fish-oil fed ($p > 0.05$, NS) animals. No deaths were observed in any animal pretreated with indomethacin or BM 13505, regardless of diet. The lack of statistical significance in mortality was not surprising given the relatively small number of animals used in this study and previous observations by our laboratory that most deaths occur later than 7 hours in this model of endotoxemia.

Fatty acid profiles of the serum phospholipid fraction after 6 weeks of feeding are shown in Table 2. Animals fed the fish oil-enriched diet had significantly increased levels of N-3 fatty acids compared to safflower oil-fed guinea pigs, with an N-3 to N-6 fatty acid ratio of approximately 1. Safflower oil-fed animals had a significant increase in the essential fatty acid linoleic acid compared to fish oil-fed animals but virtually were devoid of N-3 fatty acids in plasma phospholipid.

Figures lA to 4B show arterial blood gas profiles after endotoxin infusion in guinea pigs fed fish or safflower oil-enriched diets. In each figure 'A' represents safflower oil-fed animals and 'B' represents fish oil-fed animals given various infusions. After initiation of the endotoxin infusion, safflower oil-fed animals developed an initial respiratory alkalosis followed by metabolic acidosis as demonstrated by a significant decreases in blood pH, $paCO_2$, and $HCO_3$ ($p < 0.05$) with a concomitant increase in $PO_2$ ($p < 0.05$) compared to controls. Fish oil-fed animals, however, developed a mild respiratory alkalosis (significant rise in $PaO_2$ with a nonsignificant rise in pH at hour 3) in response to endotoxin, which normalized by the fifth hour of infusion. Pretreatment with indomethacin or BM 13505 had similar effects to N-3 fatty acid feeding in ameliorating the development of metabolic acidosis in safflower oil-fed animals, suggesting the role of prostaglandins and especially thromboxane in the sequellae of endotoxemia (Figs. 1A to 4A).

Plasma lactate determined at the end of the endotoxin infusion are shown in Figure 5. Safflower oil-fed animals had a sevenfold increase in lactate compared with saline controls ($p < 0.01$) and a threefold increase compared to fish oil-fed animals ($p < 0.01$). The increase in lactate in safflower oil-fed animals was associated with the development of acidemia (Fig. 1A). The mild elevation in plasma lactate in animals fed N-3 fatty acids and infused with endotoxin was not associated with a decrease in blood pH. Infusion of indomethacin significantly reduced the amount of lactate formed in safflower oil-fed animals given endotoxin but had no additive effect in fish oil-fed animals. Administration of BM 13505 was only partially

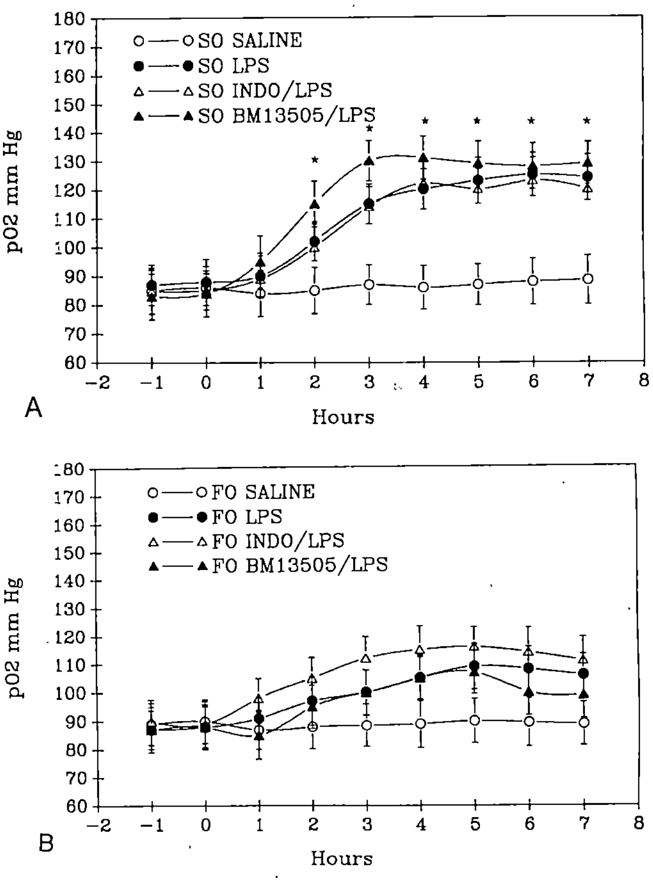


FIG. 3A and B. See Figure 1 for explanation of abbreviations.

effective in reducing lactate levels, which remained significantly above control (5.2 *versus* 1.0 mmol/L [millimolar]). The infusion of dichloroacetic acid had no effect to lower blood lactate in either group receiving endotoxin, which suggests either that PDH was not inhibited or that the dose infused was inadequate.[30]

Histologic examination of samples of lung taken from both safflower oil- and fish oil-fed animals receiving endotoxin are shown in Figures 6 and 7. Safflower oil-fed animals developed a diffuse interstitial pneumonia with increased neutrophils and intravascular congestion (Fig. 6). Fish oil-fed animals infused with endotoxin demonstrated intravascular congestion in the lungs without infiltrate (Fig. 7). The increased blood in the lungs was thought to be artifact from the time the animals were killed because all animals showed similar amounts of congestion, regardless of diet or infusion regimen. The figures shown are representative samples of the series and were picked at random by the pathologist. All other tissue samples were diagnosed as 'normal' and comparable between groups, with the exception of liver, which showed mild fatty infiltration in both dietary groups. Fibrin staining failed to reveal any evidence of microemboli in any tissue.

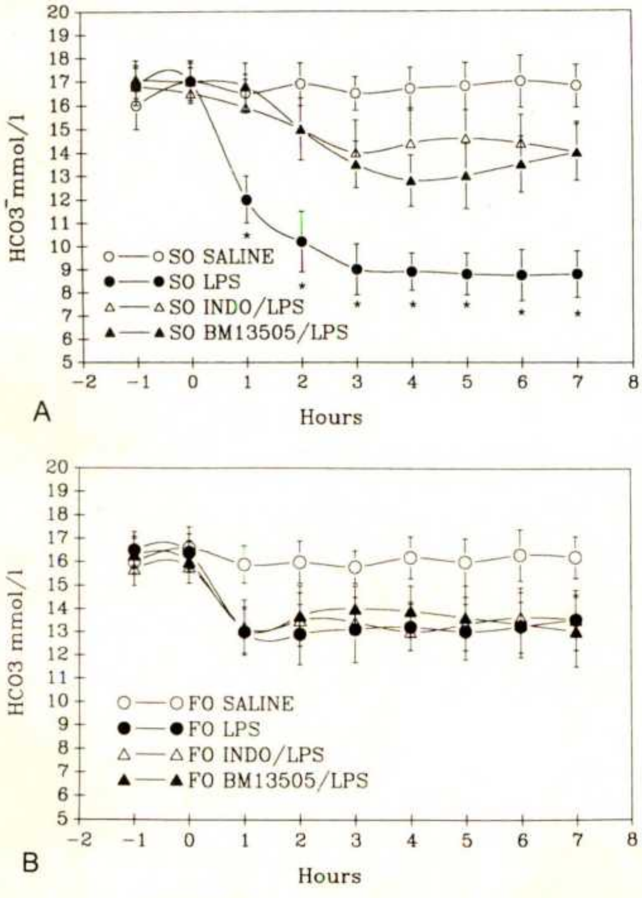


FIG. 4A and B. See Figure 1 for explanation of abbreviations.

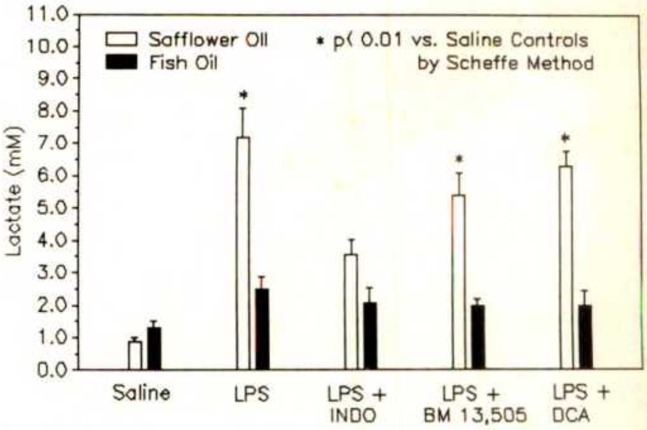


FIG. 5. Plasma lactate values after endotoxin or saline infusion in fish or safflower fed animals. Open bars, safflower oil fed; closed bars, fish oil fed. The infusion regimens are located below each pair of bars; SALINE, LPS = Endotoxin, LPS + INDO = Endotoxin + Indomethacin, LPS + BM 13505 = Endotoxin + Thromboxane Receptor Blocker, and LPS + DCA = Endotoxin + Dichloracetic acid. Lactates were determined enzymatically using a purchased kit. Safflower oil-fed animals infused with endotoxin had a sevenfold increase in lactate levels over control and twice those in fish oil-fed animals infused with endotoxin ($p < 0.05$). Pretreatment with indomethacin ameliorated the response in safflower oil-fed animals but had no potentiating effect in fish oil-fed animals. Pretreatment with the thromboxane receptor blocker ameliorated the development of lactic acidemia (Fig. 1A) but only had a marginal effect to lower lactate levels. Administration of dichloracetic acid (DCA) had no effect in either group, which suggests either PDH was not inhibited or an inadequate dose was used. Larger doses of DCA were found to be toxic. Values are mean ± SEM.

The alveolar-arterial (A-a) gradient is shown in Table 3. No significant differences in the A-a gradient were observed during the baseline period or after 7 hours of endotoxin infusion. This suggests that lung function was not severely compromised during the initial period of endotoxemia, despite obvious differences in lung morphology.

To understand better the mechanism of the protective effect of N-3 fatty acid feeding in ameliorating lactic acidosis, blood pressure, blood flow distribution, cardiac output, and tissue perfusion were assessed and are summarized in Tables 4 and 5 and Figures 8 and 9. Infusion of endotoxin caused an initial hypotension, regardless of diet (ANOVA $p < 0.05$) and normalized by the end of the infusion period (Table 4). During this period, heart rate increased significantly and remained elevated throughout the infusion period in animals receiving endotoxin.

The percentages of cardiac output perfusing each gram of various tissues are shown in Figure 8 and Table 5 (see also equation 1 above). Endotoxin infusion caused a significant decrease in the percentage perfusion of skin and muscle, regardless of dietary intake. However, in muscle, the decrement in perfusion was less in animals pretreated with N-3 fatty acids compared to safflower oil-fed animals (Fig. 8). Decreased perfusion in skin and muscle was as-

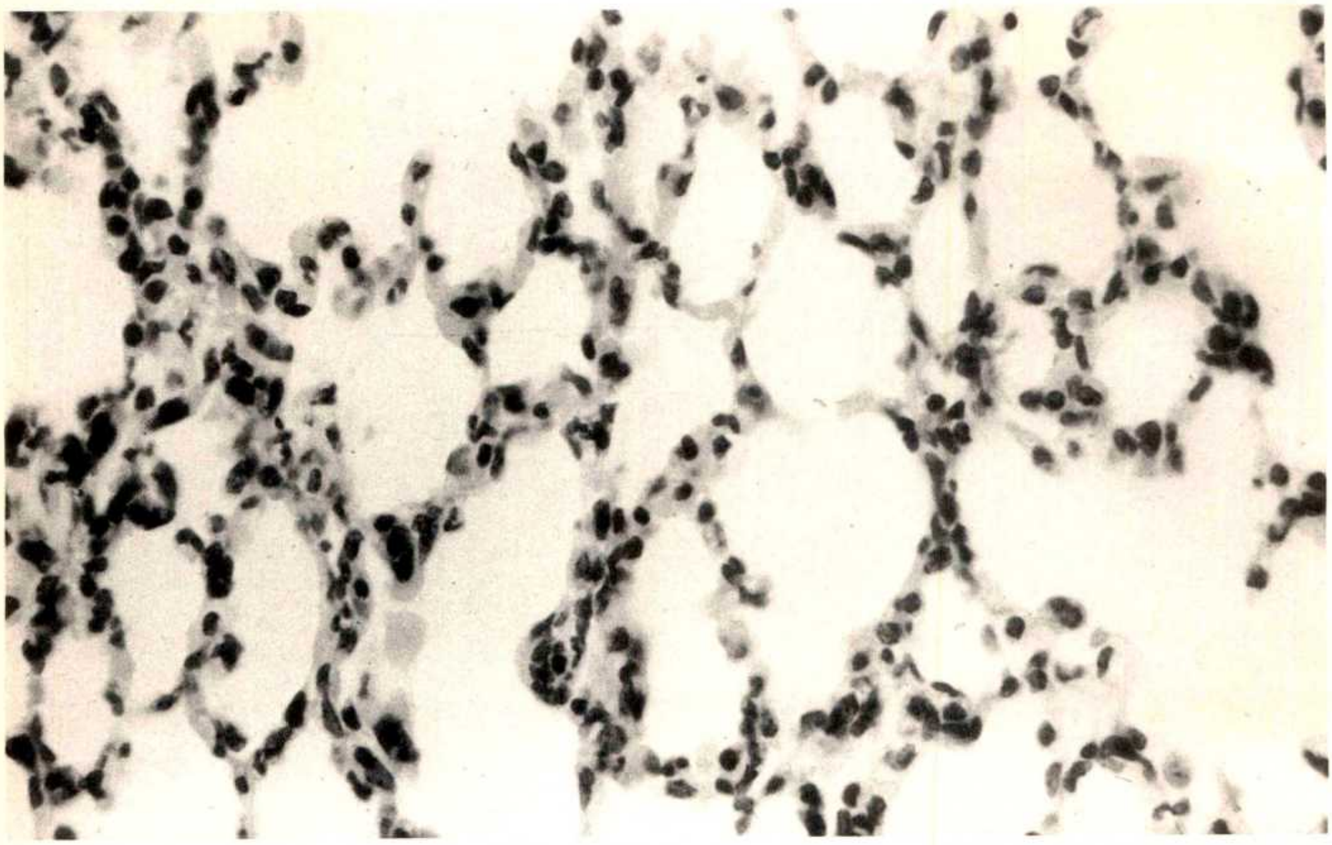


FIG. 6. Lung histology of guinea pig fed safflower oil and infused with endotoxin. Lungs were harvested after inflation with 15 mL buffered formalin *via* a catheter placed in the trachea. Tissue was stained with hematoxylin and eosin and magnified ×40 before photographing. This lung demonstrates a widespread interstitial pneumonia with many polymorphonuclear leukocytes.

sociated with a concomitant increase in splanchnic percentage perfusion (Table 5). The percentage of cardiac output perfusing kidneys was unaltered in either dietary group.

Cardiac output and the actual perfusion (calculated as the product of cardiac output and percentage perfusion) of skin and muscle tissue ($\mu$L/min/g tissue) is shown in Figure 9. Cardiac output was not significantly different among groups, regardless of dietary intake or infusion regimen. Safflower oil-fed animals had significant reductions in both skin and muscle perfusion compared to controls. Fish oil-fed animals infused with endotoxin had moderate but insignificant reductions in skin and muscle perfusion.

## Discussion

Septic shock develops as a complication of overwhelming infection. During the latter stages of sepsis, the host response is characterized by a clinical toxicity including fever, tachycardia, tachypnea, volume depletion, hypotension, lactic acidosis, mental obtundation, and eventual death associated with elevated levels of cytokines IL-1 and TNF. The exact role of cytokines during sepsis is unclear but they have many direct effects on cells and extend their influence through the activation of inflammatory pathways such as the prostaglandin/leukotriene cascade, and protein kinase C.[33,34] Several studies established that metabolites of arachidonic acid, particularly thromboxane $A_2$, may play a significant role in the sequelae of endotoxemia.[7,8,35,36] Systemic inhibition of thromboxane $A_2$ was shown to improve perfusion after trauma and sepsis,[37,38] and arachidonic acid depletion resulting in reduced thromboxane formation improved survival in a model of septic shock,[12] However systemic inhibition of thromboxane or cyclo-oxygenase can be complicated by a reorientation of eicosanoid metabolism, which may alter the finely tuned agonist–antagonist interaction with detrimental effects.[16]

Alteration of eicosanoid metabolism with diets enriched with N-3 fatty acids has theoretical advantages over pharmacologic means because there is simultaneous down regulation of both prostaglandin and leukotriene metabolism.[25–27] Therefore the administration of marine oils may be useful in attenuating the inflammatory response in situations in which the response may become counterproductive, as in the malnourished host or in adult respiratory distress syndrome (ARDS).[39] Indeed the im-

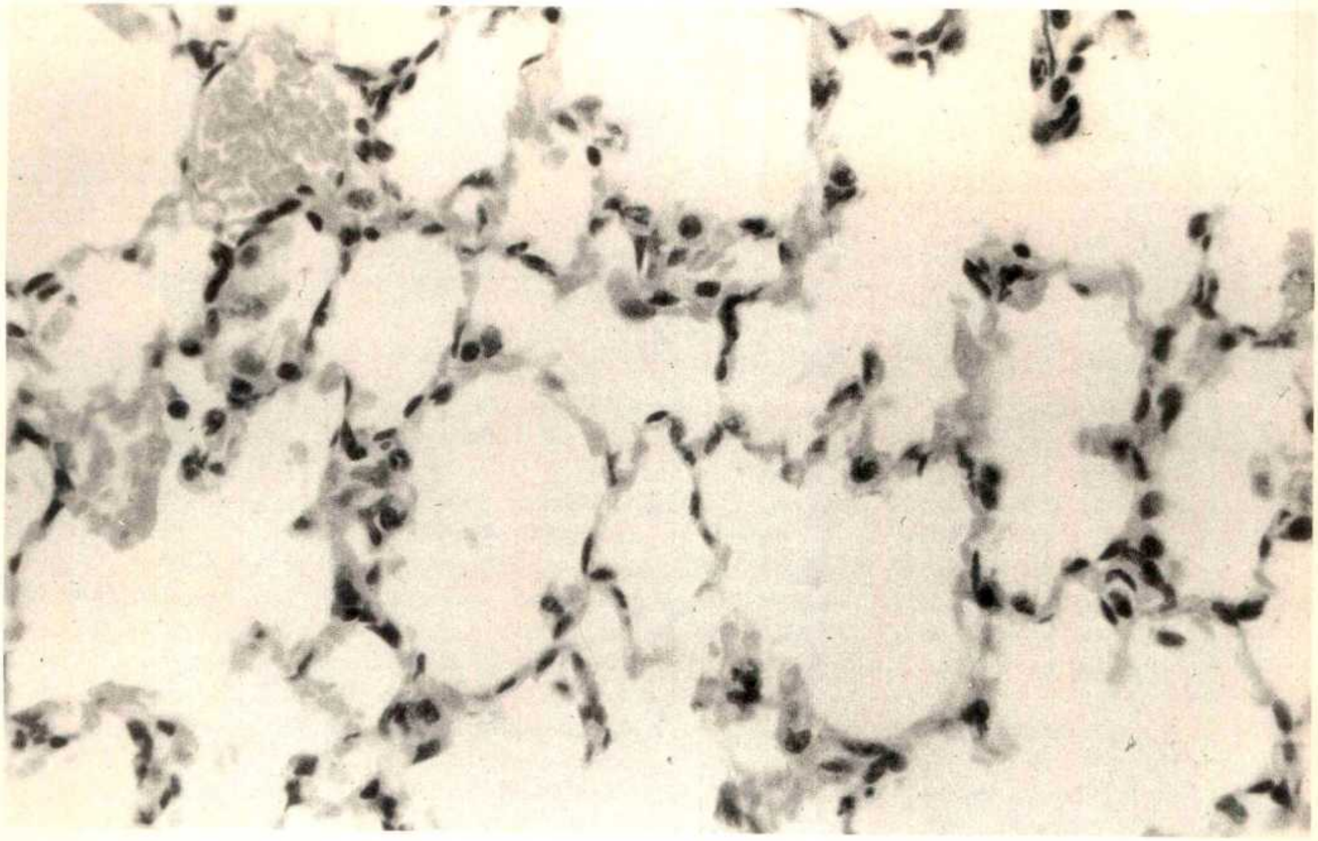


FIG. 7. Lung histology of guinea pig fed menhaden oil and infused with endotoxin. Lung tissue was processed as in previous figure. Diagnosis by a 'blinded' pathologists was 'normal' lung morphology with slight pulmonary congestion. Pulmonary congestion is most likely to be artifact as the result of killing the animal.

proved lung morphology observed in fish oil-fed *versus* safflower oil-fed animals given endotoxin may suggest a role for N-3 fatty acid feeding in attenuating the progression of ARDS. This is supported by the work of Lee et al.,[27] who demonstrated significant reduction in neutrophil chemotaxis and aggregation after fish oil feeding. However it is still unclear if the impressive biochemical effects of fish oil feeding observed *in vitro* in that study and *in vivo* in the present investigation will necessarily translate into improved clinical outcome.

TABLE 3. *Alveolar-arterial (A-a) Gradient Before and After Endotoxin Infusion*

| Diet/Treatment | Baseline mmHg | Hour 7 mmHg |
|---|---|---|
| Fish/saline | 43.0 ± 4.6 | 41.1 ± 4.9 |
| Safflower/saline | 43.1 ± 3.8 | 43.1 ± 4.5 |
| Fish/endotoxin | 38.9 ± 2.8 | 31.3 ± 5.5 |
| Safflower/endotoxin | 35.3 ± 3.0 | 32.1 ± 7.6 |

The alveolar-arterial gradient was calculated from the equation $pAO_2$-$paO_2$, where $pAO_2$ is the partial pressure of oxygen in the alveolar space and is calculated by the following equation: $pAO_2 = (PB\text{-}pH_2O)(FIO_2)\text{-}(paCO_2)/R$ and $paO_2$ is the partial pressure of oxygen in arterial blood. PB, barometric pressure; $pH_2O$, 47 mmHg, $FIO_2 = 0.21$, and $R = 0.8$. Results are expressed as mean ± SEM. No statistical differences were noted in the A-a gradient before or after endotoxin infusion, despite obvious changes in lung morphology.

In this study dietary pretreatment with N-3 fatty acids ameliorated the lactic acidosis induced by endotoxin. The reduction in lactate concentration was associated with improved microvascular perfusion in muscle as determined by radiolabeled microspheres, which is consistent with improved aerobic metabolism that would limit lactate production. An alternative explanation is that improved lactate clearance rather than decreased production was responsible for the reduced lactate levels. Although this hypothesis was not specifically explored in the present study, there was a slight but insignificant increase in splanchnic perfusion in fish oil-fed animals, raising the possibility of increased flow to the liver where lactate clearance occurs. This may explain some part of the results reported here, but future studies will be needed to explore formally the influence of fish oil feeding on lactate clearance.

Administration of indomethacin and, to a lesser extent, thromboxane receptor blocker were effective in attenuating lactic acidosis when given before endotoxin. This confirms the relative importance of cyclo-oxygenase products in the pathogenesis of endotoxin shock. The reduced ef-

TABLE 4. *Mean Arterial Blood Pressure During Endotoxin Infusion*

| Time (hrs) | −1 | 0 | 1 | 3 | 5 | 7 |
|---|---|---|---|---|---|---|
| SO SAL | 56 ± 2 | 54 ± 3 | 52 ± 2 | 50 ± 3 | 52 ± 3 | 53 ± 2 |
| SO LPS | 53 ± 3 | 52 ± 2 | 34 ± 5* | 30 ± 4* | 46 ± 4 | 47 ± 5 |
| FO SAL | 54 ± 2 | 55 ± 3 | 53 ± 4 | 51 ± 2 | 53 ± 3 | 54 ± 3 |
| FO LPS | 51 ± 2 | 52 ± 3 | 30 ± 5* | 31 ± 6* | 45 ± 6 | 46 ± 5 |

SO SAL, safflower oil fed and infused with saline; SO LPS, safflower oil fed and infused with endotoxin (0.5 mg/kg/hr); FO, fish oil fed. Arterial pressure was monitored using a multi-channel polygraph interfaced with pressure transducers connected with indwelling arterial catheters in the carotid artery. The transducers were calibrated and checked before each measurement. LPS caused transient hypotension which resolved by the end of the endotoxin infusion. Data are mean ± SEM. * = $p < 0.05$ *vs.* saline in the same group.

ficacy of the thromboxane receptor blocker compared to indomethacin or N-3 fatty acid feeding in this regard suggests that other prostaglandin products (*i.e.*, $PGG_2$, $PGH_2$) also play a role in the sequelae of endotoxemia.[24]

The pathogenesis of septic lactic acidosis is explained more easily when there is clinical evidence of tissue ischemia or hypoxemia. Under these circumstances oxygen delivery and consumption are flow dependent.[40] LaLonde et al.[11] demonstrated improved oxygen delivery and blood flow distribution following thromboxane antagonism after burn injury. Our data are consistent with the hypothesis that fish oil feeding may be improving oxygen delivery to tissues by relieving the intense microvascular vasoconstriction associated with endotoxemia.[7,8] However lactic acidosis also has been observed during hyperdynamic septic states when there is increased cardiac output and oxygen consumption,[41] adequate tissue perfusion,[42] and maintenance of normal high-energy phosphate levels in muscle and liver.[43] Elevations in serum lactate observed during hyperdynamic septic states may be the result of a defect in the oxidation of pyruvate rather than a deficit in oxygen availability.

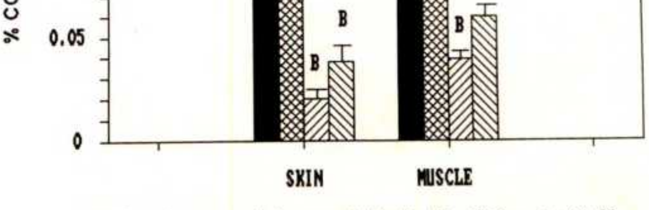
Pyruvate oxidation is regulated by the PDH complex. Previous studies have shown that gram-negative sepsis leads to inactivation of PDH with elevation of plasma lactate concentrations to 3.0 to 4.0 mmol/L range in the absence of significant tissue hypoxia.[43] However elevations of lactate more than 4 mmol/L are undoubtedly related to local hypoxia and cannot be explained by PDH inhibition alone.[44] In this study the failure of dichloroacetic acid to lower lactate levels in both safflower oil-fed and fish oil-fed animals could mean that PDH was not inhibited, and therefore DCA would not be expected to have an effect, or conversely that the dose given was not adequate for the guinea pig. The dose used was based on the amount used in dogs, which was 10 times higher than doses used in humans.[30] Trials with higher doses in the guinea pig were found to be toxic and therefore were abandoned.

TABLE 5. *Percentage Perfusion of Visceral Organs*

| Diet/Treatment | Renal % | Spleen % | Bowel % |
|---|---|---|---|
| Fish/saline | 10.0 ± 0.9 | 2.1 ± 0.2 | 18.8 ± 2.0 |
| Safflower/saline | 11.3 ± 1.0 | 2.3 ± 0.3 | 17.2 ± 1.5 |
| Fish/endotoxin | 9.8 ± 1.4 | 2.0 ± 0.7 | 22.8 ± 2.0 |
| Safflower/endotoxin | 9.8 ± 1.0 | 1.8 ± 0.8 | 32.7 ± 8.5 |

The percentage perfusion of tissues was estimated using radiolabeled microspheres injected at the end of the 7-hour endotoxin infusion. Data represent the percentage of cardiac output perfusing each tissue. Renal represents the total for both kidneys. Data are expressed as mean ± SEM.

Animals fed enteral diets enriched with safflower oil and infused with endotoxin developed a significant lactic acidosis despite an adequate systemic arterial $pO_2$, cardiac output, and blood pressure. The moderate decrease in mean systolic pressure and tachycardia observed initially after endotoxin infusion is consistent with the hyperdynamic phase of sepsis. In a state of vasodilatation, as observed acutely after endotoxin infusion, an increase in cardiac output would be expected to contribute to the normalization of blood pressure. By the end of the infusion



Different superscripts are statistically different p<0.05.

FIG. 8. Percentage of cardiac output perfusing of skin and muscle. Percentage perfusion or "q" is expressed as a percent of cardiac output/g tissue as determined at the end of the endotoxin infusion using radiolabeled microspheres. Endotoxin infusion caused a significant reduction in "q," regardless of diet. However guinea pigs fed fish oil and infused with endotoxin had significantly improved muscle perfusion compared to safflower oil-fed animals ($p < 0.05$). Data are expressed as mean ± SEM.

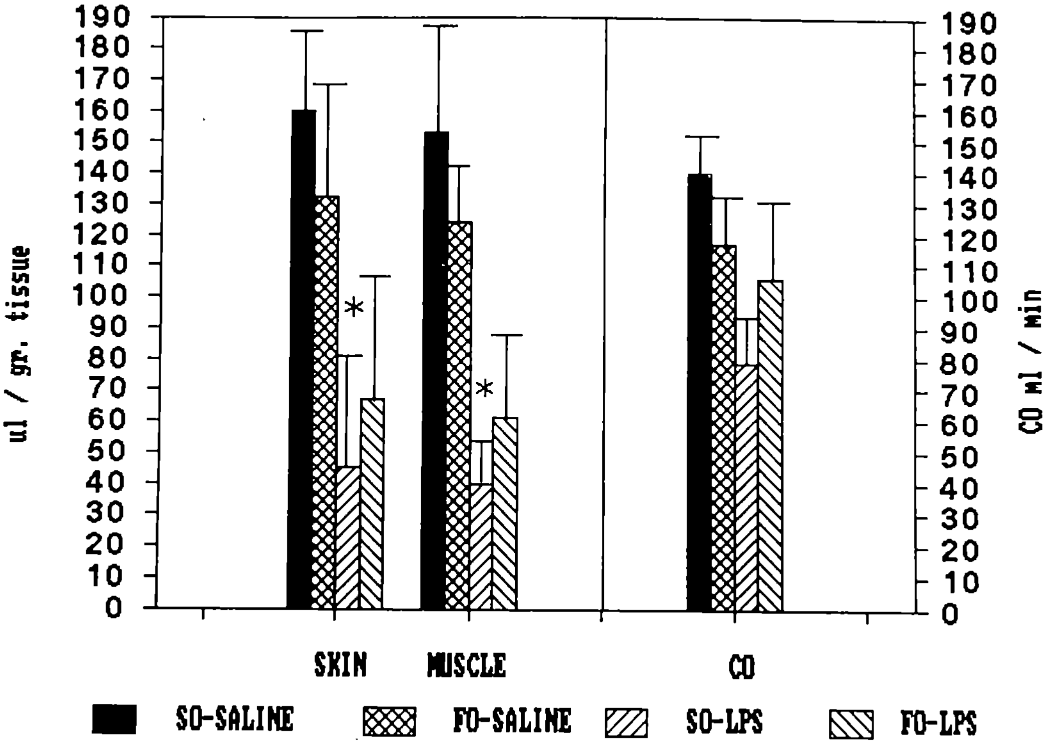


FIG. 9. Actual perfusion (μL/min/g tissue) and cardiac output. Actual perfusion was obtained by multiplying cardiac output by the percentage perfusion (q). Safflower oil-fed animals infused with endotoxin had significant reduction in perfusion of skin and muscle, which resulted from an alteration in blood flow distribution rather than a decrease in cardiac output. Fish oil-fed animals had no significant decrease in tissue perfusion compared to controls. Data are shown as mean ± SD. * = $p < 0.05$ *vs.* SALINE.

period, cardiac output determined using radiolabeled microspheres demonstrated no significant change compared to control; however microvascular perfusion to skin and muscle were reduced significantly. Unfortunately determination of cardiac output and tissue perfusion with radiolabeled microspheres is limited to a single measurement in each animal. Therefore our observed 'normal' cardiac output may represent the transition between hyperdynamic and hypodynamic sepsis because preliminary studies showed that most animals exhibit rapid deterioration with death within a few hours of terminating the endotoxin infusion. Despite this concern the data demonstrate that large reductions in blood flow can occur at the tissue level despite 'normal' systemic cardiovascular function and oxygen tension. This finding is supported by the work of Bihari et al.,[45] who have reported that microvascular tissue hypoxia can occur in critically ill patients despite the presence of an apparently adequate systemic blood flow, pressure, and arterial oxygen tension.

The effect of N-3 fatty acids on eicosanoid formation has been established clearly.[9,19,22,25,27] Recent data show that diets enriched with N-3 fatty acids also can alter monokine production to endotoxin stimulation in both experimental animals and humans.[46,47] Endres and coworkers[48] demonstrated that N-3 fatty acid supplementation in healthy volunteers can reduce significantly the amount of IL-1 and TNF formed after endotoxin challenge. This is significant because TNF has been shown to be a key mediator of many of the metabolic responses associated with sepsis and endotoxemia. Thus N-3 fatty acid feeding can alter the response to endotoxin at several levels of control and may help explain its effectiveness relative to pharmacologic modalities (*i.e.*, indomethacin, thromboxane blockers, and so on). Furthermore, unlike pharmacologic therapies that usually are administered after the initiating insult has occurred and therefore are usually less effective, dietary manipulation can be commenced safely as part of the daily routine. Certainly, to the extent that release of cytokines is diminished by fish oil feeding, this effect would only be seen with pretreatment.

N-3 fatty acid supplementation may be a useful adjunct to current therapy primarily in reducing the development and consequences of septic shock syndromes. The improved tissue perfusion observed in the absence of significant changes in cardiac output suggests that slight changes in blood flow at the tissue level can have far-reaching effects that may extend to influences on clinical outcome. Given the complicated network of efferent signals involved (*i.e.*, monokines and eicosanoid metabolites), future studies should define more precisely the impact N-3 fatty acids may have on cellular and intermediary metabolism.

## References

1. Berry LJ. Bacterial toxins. CRC Crit Rev Toxicol 1977; 5:239–247.
2. Visscher MB. Shock with particular reference to endotoxin shock. Postgrad Med 1958; 23:545–554.
3. Weil MH, Maclean LD, Visscher MB, Spink WW. Studies on circulatory changes in the dog produced by endotoxin gram-negative microorganisms. J Clin Invest 1956; 35:1191–1196.

4. Morrison DC, Ulevitch RJ. The effects of bacterial endotoxins on host mediation systems. Am J Pathol 1978; 93:526–530.
5. Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1986; 234:470–474.
6. Starnes HF, Warren RS, Jeevanandam M, et al. Tumor necrosis factor and the acute metabolic response to tissue injury in man. J Clin Invest 1988; 82:1321–1325.
7. Wise WC, Cook JA, Halushka PV. Implications for thromboxane $A_2$ in the pathogenesis of endotoxin shock. *In* Schumer W, Spitzer JJ, Marshall BE, eds. Advances in Shock Research 1980; 6:83–85.
8. Collier JG, Herman AG, Vane JR. Appearance of prostaglandin in the renal venous blood of dogs in response to acute systemic hypotension produced by bleeding or endotoxin. J Physiol 1973; 230:19–23.
9. Pomposelli JJ, Mascioli EA, Bistrian BR, et al. Attenuation of the febrile response in guinea pigs by fish oil enriched diets. J Paren Ent Nut 1989; 13(2):136–140.
10. Paterson IS, Klausner JM, Goldman G, et al. Thromboxane mediates the ischemia-induced neutrophil oxidative burst. Surgery 1989; 106(2):224–229.
11. LaLonde C, Demling RH. Inhibition of thromboxane synthetase accentuates hemodynamic instability and burn edema in the anesthetized sheep model. Surgery 1989; 105:638–644.
12. Cook JA, Wise WC, Knapp DR, Halushka PV. Essential fatty acid deficient rats: a new model for evaluating arachidonate metabolism in shock. *In* Schumar W, Spitzer JJ, Marshall BE, eds. Advances in Shock Research 1980; 6:93–96.
13. Furman BL, McKechnie K, Parratt JR. Failure of drugs that selectively inhibit thromboxane synthesis to modify endotoxin shock in concious rats. Br J Pharm 1984; 82(1):289–294.
14. McIntyre BA, Philips RB. Effect of nonsteroidal anti-inflammatory agents on platelet function and prostaglandin synthesis in vitro. Thrombosis Res 1977; 12:67–70.
15. Yoshimoto T, Yamamoto S, Hayaishi O. Selective inhibition of prostaglandin endoperoxide thromboxane isomerase by 1-carboxyalkyl-imadazoles. Prostaglandins 1978; 16:529–533.
16. Vermylen J, Deckmyn H. Reorientation of prostaglandin endoperoxide metabolism by a thromboxane synthetase inhibitor: in vitro and clinical observations. Br J Clin Pharm 1983; 15:175–180.
17. Hamberg M, Svensson J, Samuelsson B. Prostaglandin endoperoxides. A new concept concerning the mode of action and release of prostaglandins. Proc Natl Acad Sci USA 1974; 71:3824–3829.
18. Dyerberg J, Bang HO. A hypothesis on the development of acute myocardial infarction in Greenlanders. J Clin Lab Invest 1982; 42(161):7–13.
19. Bang HO, Dyerberg J. The bleeding tendency in Greenland Eskimos. Dan Med Bull 1980; 27:202–205.
20. Kromhout D, Bosschieter EB, Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985; 12(19):1205–1209.
21. Sanders TAB, Roshani F. The influence of different types of w-3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. Clin Sci 1983; 64:91–99.
22. Schacky CV, Fisher S, Weber PC. Long term effects of dietary marine w-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest 1985; 76:1626–1631.
23. Fischer S, Weber PC. Prostaglandin $I_3$ is formed *in vivo* in man after dietary eicosapentaenoic acid. Nature 1984; 307:165–168.
24. Hamberg M, Svensson J, Wakabayshi T, Samuelsson B. Isolation of and structure of two prostaglandin endoperoxides that cause aggregation. Proc Nat Acad Sci USA 1974; 71:345–350.
25. Fischer S, Weber PC. Thromboxane $A_3$ is formed in human platelets after dietary eicosapentaenoic acid. Biochem Biophys Res Commun 1983; 116:1091–1099.
26. Needleman P, Raz A, Minkes MS, et al. Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. Proc Natl Acad Sci USA 1979; 76:944–948.
27. Lee TH, Mencia-Huerta JM, Shih C, et al. Characterization and biologic properties of 5,12-dihydroxy derivatives of eicosapentaenoic acid, including leukotriene $B_5$ and the double lipoxygenase product. J Biol Chem 1984; 259(4):2383–2389.
28. Moncada S, Gryglewski R, Bunting S, et al. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 1976; 263:663–665.
29. Mascioli EA, Leader L, Flores E, et al. Enhanced survival to endotoxin in guinea pigs fed IV fish oil emulsion. Lipids 1988; 23(6):623–625.
30. Stacpoole PW, Harmon EM, Curry SH, et al. Treatment of lactic acidosis with dichloroacetate. N Engl J Med 1983; 309:390–396.
31. Malik AB, Kaplan JE, Saba TM. Reference sample method for cardiac output and regional blood flow determinations. J Appl Physiol 1976; 40:472–475.
32. Laughlin MH, Mohrman SJ, Armstrong RB. Muscular blood flow distribution patterns in the hindlimb of swimming rats. Am J Physiol 1984; 246:H398–H403.
33. Elias JA, Gustillo K, Baeder W, Freundlich B. Synergystic stimulation of fibroblast prostaglandin production by recombinant interleukin-1 and tumor necrosis factor. J Immunol 1987; 138:3812–3816.
34. Magnuson DK, Maier RV, Pohlman TH. Protein kinase C: a potential pathway of endothelial cell activation by endotoxin, tumor necrosis factor, and interleukin-1. Surgery 1989; 106:216–223.
35. Watkins D, Huttemeier P, Kong D, Peterson M. Thromboxane and pulmonary hypertension following E. coli endotoxin infusion in sheep: effect of an imidazole derivative. Prostaglandins 1982; 23:273–285.
36. Flynn J. The role of arachidonic acid metabolites in endotoxin shock II: involvement of prostanoids and thromboxanes. *In* Hinshaw LB, ed. Handbook of Endotoxin. Amsterdam: Elsevier Science Publishers, 1985.
37. Kay S, Green C. The effect of a novel thromboxane synthetase inhibitor dazmegrel (UK 38485) on random pattern skin flaps in the rat. Br J Plast Surg 1986; 39:361–363.
38. Lorenz R, Fischer S, Wober W, Weber P. Effects on prostanoid formation and pharmacokinetics of dazmegrel (UK 38485), a novel thromboxane synthetase inhibitor in man. Biochem Pharmacol 1986; 35:761–766.
39. Ognibene FP, Martin SE, Parker MM, et al. Adult respiratory distress syndrome in patients with severe neutropenia. N Engl J Med 1986; 315:547–551.
40. Rackow EC, Astiz ME, Weil MH. Cellular oxygen metabolism during sepsis and shock. J Am Med Assoc 1988; 259(13):1989–1993.
41. Siegal JH, Vary TC. Sepsis, abnormal metabolic control and multiple organ failure syndrome. *In* Siegal JH, ed. Trauma: Emergency Surgery and Critical Care. New York: Curchill Livingston, 1987, pp 411–502.
42. Fish RE, Lang CH, Spitzer JA. Regional blood flow during continuous low-dose endotoxin infusion. Circ Shock 1986; 18:267–275.
43. Vary TC, Siegal JH, Nakatani T, et al. Regulation of glucose metabolism by altered pyruvate dehydrogenase activity. Potential site of insulin resistance in sepsis. J Paren Ent Nut 1986; 10:351–355.
44. Cady LD, Weil MH, Afifi AA, et al. Quantitation of severity of critical illness with special reference to blood lactate. Crit Care Med 1973; 1:75–79.
45. Bihari D, Smithies M, Gimson A, et al. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 1987; 317(7):397–403.
46. Billiar TR, Bankey PE, Svingen BA, et al. Fatty acid intake and kupffer cell function: fish oil alters eicosanoid and monokine production to endotoxin stimulation. Surgery 1988; 104(2):343–349.
47. Endres S, Ghorbani R, Kelley VE, et al. Dietary n-3 polyunsaturated fatty acids suppress synthesis of interleukin-1 and tumor necrosis factor. N Engl J Med 1989; 320:265–271.
48. Michie HR, Spriggs DR, Manogue KR, et al. Tumor necrosis factor and endotoxin induce similar metabolic responses in human beings. Surgery 1988; 104(2):280–286.

# Immediate Enteral Feeding in Burn Patients Is Safe and Effective

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**Recent animal studies indicate that immediate enteral feeding may be beneficial in patients with major burns. Yet, largely because of the fear of complications, immediate enteral feeding is not commonly performed in patients with major burns until after the resuscitation period. The purpose of this study was to evaluate the safety and efficacy of immediate enteral tube feedings in patients with burns larger than 20% of their body surface area. The daily intake of enteral feedings begun immediately (less than 6 hours) after burn was measured during the first 7 days after burn in 106 consecutive patients with a mean ± SD burn size of 40% ± 21%. The incidence of complications related to enteral feeding was low; aspiration pneumonia did not occur. Vomiting was the major complication observed and occurred 21 times in 16 patients during the 745 study days (2.8% daily incidence). The mean number of calories absorbed enterally increased daily and met the patient's calculated resting energy expenditure (REE) on day 3 after burn (99% ± 7% REE). The results of this study indicate that immediate enteral feeding is a safe and effective method of delivering nutritional support to burn victims with major burns.**

THE POSTBURN PERIOD is characterized by a hypermetabolic state, which, if not met, results in visceral protein loss, impaired antibacterial host defenses, and delayed wound healing.[1] Although there is no doubt that a policy of aggressive nutritional support improves survival in burn victims,[2] the optimal clinical approach to the nutritional support of the burn patient remains to be fully determined. Although there is increasing experimental evidence that enteral alimentation is beneficial,[3,4] especially if begun immediately after burn, immediate enteral feeding has not gained clinical acceptance. Instead enteral feedings generally are not begun until after the acute fluid resuscitation period is over and gastrointestinal function has returned to normal.[5] Delay in acceptance of immediate postburn enteral feeding appears to be related largely to the fear that immediate feeding will result in a higher rate of complications than delayed feeding. Therefore the purpose of this study was to evaluate the safety and efficacy of immediate enteral feeding begun within 6 hours of injury in patients with major burn injuries.

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## Patient Population and Methods

The hospital and nutritional records of all patients admitted to the Louisiana State University–Shreveport Burn Center between January 1986 and January 1989 were reviewed to identify the study group. Patients who met the following two entry criteria comprise the study group: (1) the presence of a 20% or greater total body surface-area (TBSA) burn and (2) enteral feeding begun within 6 hours of injury. During the 3-year study period, 106 of the 524 patients admitted to the Burn Center fulfilled these entry criteria. The following information was recorded for each patient: age; race; sex; total burn size, including percentage third-degree burn; and predicted mortality.[6] The demographics of this patient population are outlined in Table 1.

All patients were treated with a standard treatment regimen that was modified when necessary according to the clinical responses of each patient. This regimen consisted of fluid resuscitation based on the Parkland formula, topical antimicrobial agents, and early excision and grafting of deep partial- and full-thickness burns, with the first operation generally performed between days 3 and 6 after burn. Prophylactic antibiotics were not administered except during the perioperative period in patients undergoing burn wound excision and grafting.

Enteral feeding was began *via* a nasogastric tube within 1 hour of admission and within 6 hours of injury in all patients. The primary enteral formula used was Ensure-Plus (1.5 Kcal/mL; Ross Laboratories, Columbus, OH); however, in some very young children, infant formula was used instead of Ensure-Plus. The enteral feedings were used for stress ulcer prophylaxis and none of the patients received antacids or H2 blockers. The enteral feedings were administered as bolus gastric feedings every 2 hours. In adults and children older than 3 or 4 years old, the initial volume administered was 60 mL every 2 hours. In children younger than 3 years, the volumes varied from 30 to 50 mL every 2 hours. At the end of each 2-hour period, before the administration of the next bolus feeding, the gastric residual was aspirated, the volume recorded,

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TABLE 1. *Demographics of 107 Burn Patients*

| Group | n | Age | % TBSA | % 3rd | % Inhalation |
|---|---|---|---|---|---|
| All patients | 106 | 32 ± 23 | 40 ± 21% | 16 ± 17 | 14 |
| All survivors | 87 | 30 ± 22 | 35 ± 14 | 12 ± 13 | 11 |
| All deaths | 19 | 43 ± 26 | 63 ± 26 | 34 ± 23 | 26 |
| Adults only | 79 | 42 ± 19 | 43 ± 21 | 18 ± 19 | 14 |
| Adult survivors | 63 | 39 ± 18 | 37 ± 15 | 13 ± 14 | 11 |
| Adult deaths | 16 | 51 ± 20 | 67 ± 25 | 39 ± 22 | 25 |
| Pediatrics (≤12 yrs) | 27 | 3.8 ± 3.6 | 33 ± 12 | 12 ± 10 | 15 |
| Pediatric survivors | 24 | 4.2 ± 3.7 | 32 ± 10 | 12 ± 10 | 13 |
| Pediatric deaths | 3 | 1.0 ± 0 | 41 ± 23 | 11 ± 12 | 33 |

Sixty-nine of the patients were male; 50.5% were caucasian, and 49.5% were black. All data expressed as mean ± SD.

TBSA, total body surface area; % 3rd, percentage third-degree burn.

and then this residual was discarded. By monitoring the gastric residuals, it was possible to determine how much of the previously administered tube feeding had been absorbed as well as to assess gastric emptying. During the second 24-hour postburn period, the volume of tube feedings was increased from 60 mL every 2 hours to 90 to 120 mL every 2 hours in adults and doubled in children. From postburn day three and thereafter, the volume of tube feeding administered varied based on the patient's calculated nutritional needs (Table 2) and the ability of each patient to absorb the administered tube feedings. In general the maximal volume of tube feedings averaged 180 to 240 mL every 2 hours in the adult patients and varied from 100 to 200 mL every 2 hours in the pediatric patients. When enteral feedings did not meet the patient's calculated nutritional requirements, peripheral hyperalimentation was begun on the third or fourth postburn day. The peripheral alimentation solution generally consisted of 10% glucose and 4.4% amino acids, although lower levels of glucose sometimes were used (5% to 7.5% glucose).

The daily enteral caloric intake for each patient was computed by subtracting the gastric residual volume from the volume of tube feedings administered. If anything this approach underestimates the amount of enterally administered nutrients absorbed because the gastric residual consists of both tube feedings and gastric secretions. To determine the efficacy of this immediate enteral nutrient administration regimen in meeting the patient's daily caloric needs, the total number of enteral calories absorbed per day during the first postburn week was recorded and compared against the patient's estimated resting energy expenditure (REE). Resting energy expenditure was calculated from the Harris–Benedict equation[7] in adults and from an age- and weight-based nomogram in children.[8] Some patients could resume normal enteral feeding and did not require tube feedings during the entire 7-day study period. These patients were terminated from the study on the day that tube feedings were no longer the primary source of enteral nutrient administration. To investigate the incidence of complications related to this regimen of immediate enteral feeding, the incidence of vomiting, gastrointestinal hemorrhage, and pulmonary aspiration were determined daily for each patient.

TABLE 2. *Estimated Nutritional Requirements*

| Burn Size | REE* | Protein |
|---|---|---|
| 20% to 30% TBSA | 1.5 X REE | 1.0–1.5 g/kg |
| 31% to 50% TBSA | 1.5–2.0 X REE | 1.5–2.0 g/kg |
| >50% TBSA | 2 X REE | 2.0–2.3 g/kg |

* Level of resting energy expenditure (REE) based on Harris–Benedict equation in adults or age- and weight-based nomogram in children.

TBSA, total body surface area.

### *Statistical Analysis*

Statistical analysis was performed on a Northgate System computer (Northgate Computor Systems, Inc., Plymouth, MI) using the statistical program Primer of Biostatistics: The Program. All values are expressed as mean ± SE unless otherwise noted. Differences between groups were analyzed by chi square for noncontinuous data and analysis of variance for continuous data. Multimean analysis between groups was performed by Student-Newman-Keuls test.

## Results

The policy of immediate enteral feeding was well tolerated, with 82% of the patients absorbing at least a portion of their tube feedings on the day of injury (Table 3). The percentage of patients tolerating their tube feedings increased daily until day 4, when it reached 95% and remained at this level for the remaining 3 study days (Table 3). The most common complication observed was vomiting (21 episodes), which occurred in 16 of the 106 pa-

TABLE 3. *Percentage of Patients Tolerating Tube Feedings*

| Age (yrs) | n | Mean Burn Size (%) | Postburn Day 1 (%) | 2 (%) | 3 (%) | 4 (%) |
|---|---|---|---|---|---|---|
| 1–4 | 18 | 35 | 94 | 100 | 100 | 100 |
| 5–12 | 9 | 24 | 78 | 89 | 100 | 100 |
| 13–50 | 57 | 45 | 77 | 89 | 89 | 94 |
| 51–65 | 12 | 42 | 75 | 92 | 92 | 100 |
| >65 | 10 | 33 | 100 | 78 | 89 | 78 |
| Total | 107 | 40 | 82 | 90 | 92 | 95 |

Patients were classified as tolerating diet if they absorbed at least some of their tube feedings on that day.

tients (15%). Two of these 16 patients (3 episodes) also had evidence of blood in their nasogastric aspirate. In neither patient was the bleeding active and neither patient required transfusion for this bleeding episode. The number of daily bowel movements was not recorded; therefore no direct information is available on the effects of this feeding regimen on bowel motility. However none of the patients had their tube feedings stopped because of diarrhea. This feeding regimen did not appear to be associated with major pulmonary complications because none of the patients had clinical evidence of aspiration pneumonia.

The 16 patients who had one or more complications of enteral feeding were clinically similar to the 90 patients who did not have any complications (Table 4). This was not true when the patients were stratified according to whether they tolerated their enteral feedings during the study period. Patients were considered not to have tolerated the tube feeding if their gastric residuals were greater than the volume of the administered tube feedings on 2 or more of the 7 study days. Not surprising the patients who did not tolerate their tube feedings had larger burns and a higher actual and predicted mortality rate than those patients who did tolerate their tube feedings (Table 4). Thus the presence or development of a gastric ileus was a serious prognostic sign. Nonetheless this policy of immediate enteral feeding appeared to be well tolerated by most patients and was not associated with a high rate of complications.

To determine the efficacy of immediate enteral feeding on meeting the patient's metabolic needs, the amount of calories absorbed were quantitated. Because the basal metabolic needs of these patients varied based on their age, sex, and weight, caloric intake was normalized by expressing the amount of calories absorbed as a percentage of the patient's REE. There were minimal differences between the pediatric and adult patients in the daily amount of enteral calories absorbed when expressed as percentage REE (Table 5). Thus, in both patient age groups, immediate enteral feeding was an effective way to meet the patient's resting energy requirements. The relationship between the amount of calories absorbed and percentage REE for the adult patient population is graphically displayed in Figure 1. By day 4 the mean amount of enterally absorbed calories was more than 1800 Kcal and the mean caloric intake had exceeded the amount of calories required to meet the patient's REE.

When the patients were stratified by burn size, there was a relationship between the size of the burn and the amount of enteral calories absorbed. On each of the study days, patients with 60% or more TBSA received less enteral calories than patients with smaller burns (Fig. 2). This difference appeared to be related to a decreased ability of the patients with larger burns to tolerate their enteral feedings (higher gastric residuals). When the relationship between percentage third-degree burns and enteral feeding was analyzed, it was found that the percentage TBSA burn was a better predictor of whether the patients would tolerate their tube feedings than the percentage third-degree burns (data not shown).

Because factors in addition to burn size influence the ability of patients to tolerate the stress of a thermal injury, the patients were stratified into the following three groups according to their predicted mortality rate: (1) 0% to 19%;

TABLE 4. *Relationship Between Outcome and Complications or Tolerance to Immediate Enteral Feeding Regimen*

|  | n | Mean ± SD Burn Size | Predicted Mortality | Actual Mortality (n) |
|---|---|---|---|---|
| Complications |  |  |  |  |
| No | 90 | 39% ± 20% | 32% ± 35% | 17% (15) |
| Yes | 16 | 45% ± 21% | 38% ± 36% | 25% (4) |
| p value |  | NS | NS | NS |
| Tolerated Diet* |  |  |  |  |
| Yes | 87 | 35% ± 14% | 24% ± 28% | 9.3% (8) |
| No | 13 | 60% ± 26% | 73% ± 35% | 38.5% (5) |
| p value |  | <0.007 | <0.0001 | <0.004 |

* Patients were classified as not tolerating diet if they did not absorb at least a portion of their tube feedings on 2 or more days during the study. The six patients who died within the first 4 days of their burn injuries were excluded from analysis.

TABLE 5. *Efficacy of Tube-feeding Regimen on Meeting Daily Caloric Needs of Pediatric and Adult Patients*

| | | Postburn Day* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age (yrs) | n | 1 (%) | 2 (%) | 3 (%) | 4 (%) | 5 (%) | 6 (%) | 7 (%) |
| 0–12 | 27 | 35 ± 7 | 86 ± 10 | 121 ± 13 | 103 ± 14 | 135 ± 13 | 111 ± 13 | 134 ± 15 |
| >12 | 79 | 28 ± 4 | 62 ± 6 | 91 ± 8 | 115 ± 9 | 103 ± 9 | 115 ± 12 | 117 ± 13 |
| Total | 106 | 30 ± 4 | 69 ± 5 | 100 ± 7 | 111 ± 8 | 112 ± 8 | 113 ± 10 | 121 ± 10 |

* Data expressed as mean ± SEM of the percentage resting energy expenditure met *via* tube feeding.

(2) 20% to 50%; and (3) more than 50% predicted mortality. Factors used to compute mortality included total burn size, percentage third-degree burn, age, presence of an inhalation injury, and pre-existant pulmonary disease.[6] There was an inverse relationship between predicted mortality and amount of enteral calories absorbed that was most apparent during the first 3 days after burn (Table 6). Furthermore there was a clear difference between patients with predicted mortality rates less than 50% and patients with predicted mortality rates greater than 50% (Fig. 3). When the two groups with predicted mortality rates less than 50% were combined and compared to the patients with a predicted mortality rate greater than 50%, the patients with predicted mortality rates less than 50% absorbed more calories on each of the study days, except day 4 (Fig. 3).

## Discussion

The major finding of this study is that immediate postburn enteral feeding is a safe and effective method of delivering nutrients in both children and adults. Although other investigators have documented clinically that burn victims can be fed enterally, with the exception of McArdle et al.[9] in these previous studies the enteral feedings were delayed until after the resuscitation period was completed.[2,10,11] In a study of 12 burn patients, with burns greater than 40% TBSA, McArdle et al.[9] found that early enteral feeding (begun by the day 4 after burn) was associated with a reduced catabolic response. Furthermore nitrogen balance became positive in these patients on average 10 days after enteral feeding was instituted. In the past, one reason for not starting enteral feedings imme-

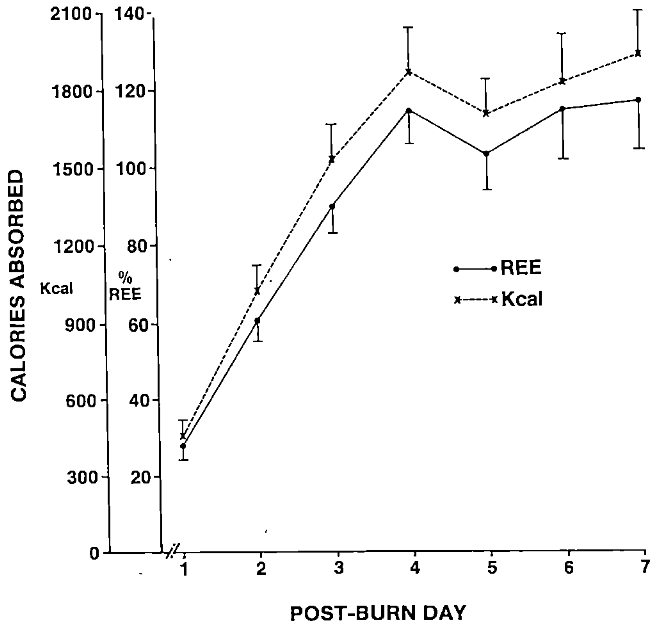

FIG. 1. Daily caloric intake of 79 adult burn victims. Data expressed as mean ± SEM percentage of estimated REE or as mean ± SEM Kcal absorbed.

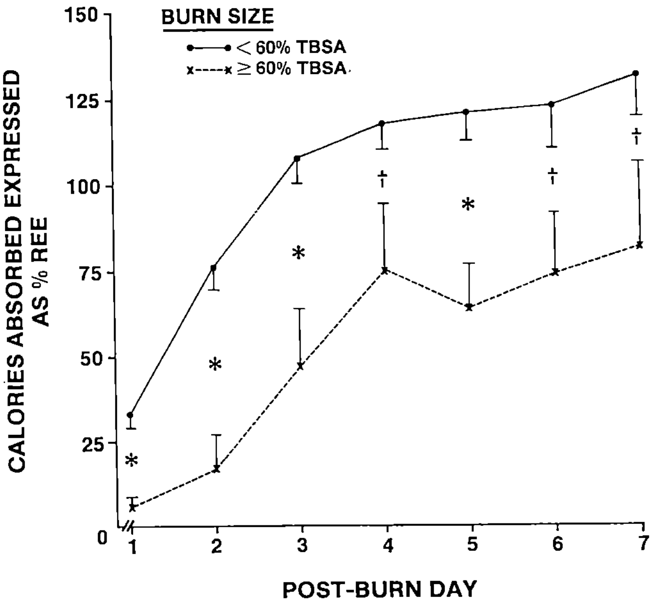

FIG. 2. Patients with burns less than 60% of their total body surface area (TBSA) absorbed more calories than patients with burns greater than 60%. Data expressed as mean ± SEM % REE. $^*p < 0.01$ and $+ p \leq 0.05$ by ANOVA.

diately after burn was the belief that the hemodynamic and cardiopulmonary aspects of burn care took priority over achieving nutritional balance in the first week after burn.[1] However this concept no longer appears valid. Instead it appears that immediate enteral feeding after burn may improve patient outcome not just by providing nutrients but by helping to maintain intestinal barrier function,[4,12] preventing bacterial translocation,[13,14] and increasing the host's ability to control a septic challenge.[2,15]

The concept that immediate post-burn enteral feeding may be beneficial was first shown experimentally by Alexander's group.[4,12] They documented that early enteral but not parenteral feeding of burned animals can attenuate markedly the hypermetabolic response to thermal injury.[4,12] Based on their studies of intestinal morphology[4] and the bacterial translocation studies of Deitch et al.,[13,14] Alexander[4] postulated that early enteral feeding may attenuate the hypermetabolic response by preserving the gut mucosal barrier and thereby preventing the translocation of bacteria or endotoxin from the gut to the portal or systemic circulation. Confirmatory human studies have been published documenting that intestinal barrier function is lost immediately after burn[16] as well as during periods of sepsis.[17] In fact, because low doses of endotoxin can increase intestinal permeability in healthy volunteers[18] and endotoxemia is relatively common in patients with major burn injuries,[19] it appears that the burn victim may be at increased risk of losing normal intestinal barrier function.

In circumstances where either enteral or parenteral nutrition can be administered, enteral nutrition appears preferable to parenteral nutrition for several biologic reasons, in addition to its superiority in terms of cost, safety, and convenience. For example enteral nutrition is superior to parenteral nutrition in maintaining gastrointestinal mass and function because the weight, mucosal height, mucosal protein and DNA content, as well as enzymatic activity of the intestines decreases in parenterally fed animals.[20] In conditions in which gastrointestinal growth is required, such as after massive small bowel resection, enteral feeding is more effective in stimulating mucosal growth and functional adaptation than the same nutrients administered parenterally.[21,22] Furthermore Kudsk et al.[15] documented that animals fed enterally survive a septic insult better than animals fed an identical diet parenterally. In fact survival from bacterial peritonitis was greater in enterally repleted than in parenterally repleted malnourished rats.[23] Thus enteral nutrients appear to exert a trophic effect on intestinal morphology and function that is not observed with standard hyperalimentation solutions. The exact reasons why enteral feedings maintain gut mass and function better than parenteral feedings is not fully known, although it appears that maintenance of mucosal mass and perhaps mucosal integrity requires the presence of specific intraluminal nutrients or substances, such as glutamine[24] or fiber.[25]

TABLE 6. *Relationship Between Predicted Mortality and Daily % REE Met by Enteral Feedings*

| Postburn Day | Predicted Mortality Rate<br>0% to 19% | <br>20% to 50% | <br>>50% |
|---|---|---|---|
| 1 | 37 ± 5† | 31 ± 8 | 14 ± 5 |
| 2 | 92 ± 7* | 54 ± 8 | 41 ± 10 |
| 3 | 129 ± 9* | 76 ± 11 | 73 ± 16 |
| 4 | 119 ± 11 | 122 ± 15 | 100 ± 15 |
| 5 | 127 ± 12† | 120 ± 10 | 82 ± 16 |
| 6 | 123 ± 15 | 132 ± 18 | 86 ± 18 |
| 7 | 130 ± 16 | 157 ± 19† | 84 ± 15 |

† $p < 0.05$ *vs.* >50% on that day. *$p < 0.05$ *vs.* other groups on that day. Data expressed as mean ± SEM.

REE, resting energy expenditure.

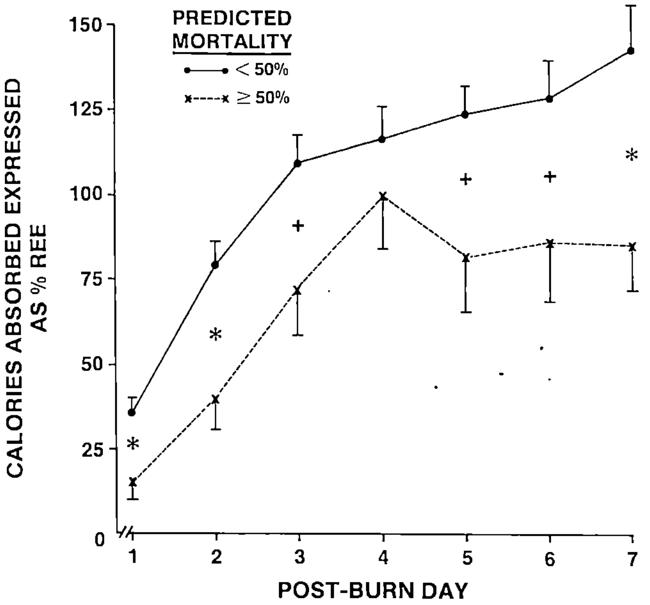

FIG. 3. Patients with a predicted morality rate less than 50% absorbed more calories than patients with a predicted mortality rate of 50% or more. Data expressed as mean ± SEM % REE. *$p < 0.01$ and + $p \leq 0.05$ by ANOVA.

We believe that a policy of immediate enteral feeding may be superior to delayed enteral feeding, even though only limited amounts of enterally administered nutrients are absorbed during the first few days after burn. This concept is based on the experimental findings that short-term starvation or total parenteral nutrition (TPN) leads to atrophy of gut tissue out of proportion to that seen in other organs.[26,27] Thus intraluminal nutrients appear to have an integral role in the maintenance of gut structure and the prevention of mucosal atrophy. Clinically the transition to an oral diet after a period of TPN is often associated with diarrhea and malabsorption, which is believed to be a direct result of mucosal atrophy. This diarrheal state, by impairing the ability of the patient to tolerate enteral feeding, may result in further limitation of enteral intake and thus promote further mucosal atrophy. Therefore it is easy to visualize a potential cycle in which starvation or TPN, by causing mucosal atrophy, predisposes to malabsorption and diarrhea and thereby impairs the ability of the patient to tolerate subsequent enteral feedings. The fact that none of our patients developed diarrhea severe enough to require cessation or modification of enteral feeding during the study period suggests that immediate feeding may improve nutrient absorption by limiting or preventing mucosal atrophy. This is not to suggest that there is not a role for parenteral nutrition to supplement enteral alimentation in these hypermetabolic patients. However we do believe that at least a portion of the daily nutrient needs of the patient should be administered enterally beginning immediately after burn.

A second finding of this study is that enteral feedings successfully prevented upper gastrointestinal bleeding and eliminated the need for antacids or H2 blockers. This second observation is similar to the results of other studies in burn patients in which different enteral feeding regimens were used.[28,29] This finding may be of clinical importance because investigators have begun to question whether the use of antacids or H2 blockers to alkalinize the stomach could be clinically deleterious. This fear is based on reports documenting that alkalinization results in bacterial colonization of the stomach and that the stomach is the primary reservoir for bacteria causing gram-negative pneumonias in mechanically ventilated patients.[30,31] Although the effect of immediate enteral feeding on the development of pneumonia was not examined in this study, we believe that an additional benefit of immediate enteral feeding is that it is an effective method of stress bleeding prophylaxis.

The postburn period is characterized by a hypermetabolic state in which accelerated substrate mobilization is required to supply energy for host defenses and wound repair. Failure to meet these metabolic needs results in visceral protein loss, impaired immune function, and delayed wound healing, which may lead to the development of multiple-organ failure. Because enteral nutrition improves the resistance to experimental infections, blunts the hypermetabolic response to thermal injury, and maintains intestinal structure and function better than parenteral nutrition, there are many biologic reasons to favor a policy of immediate enteral feeding in burn victims as well as other severely ill or injured patients. The results of this study document that immediate enteral feeding of burn patients is a safe and effective method of delivering nutrients. Future studies must be directed toward determining the optimal composition of enteral diets in these high-risk patients as well as to determine whether enteral alimentation improves outcome. We believe that these future studies are likely to be fruitful based on recent work documenting that immediate postoperative enteral nutrition is more effective than parenteral nutrition in reducing the incidence of major infectious complications in trauma victims.[32]

## References

1. Wilmore DW. Nutrition and metabolism following thermal injury. Clin Plast Surg 1974; 1:603–619.
2. Alexander JW, MacMillan BG, Stinnet JD, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg 1980; 192:505–517.
3. Deitch EA. Does the gut protect us or injure us when ill in the ICU. *In* Cerra F, ed. Perspectives in Critical Care. St. Louis, MO: Quality Medical Publishing, 1988.
4. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. Ann Surg 1984; 200:297–310.
5. Goodwin CW. Metabolism and nutrition in the thermally injured patient. Crit Care Clinic 1985; 1:97–117.
6. Zawacki BE, Azen SP, Imbus SH, Chang YC. Multifactorial probit analysis of mortality in burned patients. Ann Surg 1979; 189:1–5.
7. Harris J, Benedict F. A biometric study of basal metabolism in man. Washington, DC, Carnegie Institute, 1919.
8. Johnson HL. Energy metabolism at verious weights: Basal: Infants and Children. *In* Altman PL, Dittmer DS, eds. Metabolism. Bethesda, MD. Federation of American Societies for Experimental Biology 1968; p 344.
9. McArdle AH, Palmason C, Brown RA, et al. Early enteral feeding of patients with major burns: prevention of catabolism. Ann Plast Surg 1984; 13:396–401.
10. Bartlett RH, Allyn PA, Medley T, Wetmore N. Nutritional therapy based on postitive caloric balance in burn patients. Arch Surg 1977; 112:974–980.
11. Larkin JM, Moylan JA. Complete enteral support of thermally injured patients. Amer J Surg 1976; 131:722–724.
12. Saito H, Trocki O, Alexander JW, et al. The effect of route of nutrient administration on the nutritional state, catabolic hormone secretion, and gut mucosal integrity after burn injury. JPEN 1986; 11:1–7.
13. Deitch EA, Maejima K, Berg R. Effect of oral antibiotics and bacterial overgrowth on the translocation of the GI-tract microflora in burned rats. J Trauma 1985; 25:385–392.
14. Maejima K, Deitch EA, Berg R. Promotion by burn stress of the translocation of bacteria from the gastrointestinal tracts of mice. Arch Surg 1984; 119:166–172.
15. Kudsk KA, Stone JM, Carpenter G, Sheldon G. Enteral and parenteral feeding influences mortality after hemoglobin E coli peritonitis in normal rats. J Trauma 1983; 23:605–609.
16. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. Surgery 1990; 107:411–416.
17. Ziegler TR, Smith RJ, O'Dwyer ST, et al. Increased intestinal permeability associated with infection in burn patients. Arch Surg 1988; 123:1313–1319.
18. O'Dwyer ST, Michie HR, Ziegler TR, et al. A single dose of endotoxin

increases intestinal permeability in healthy humans. Arch Surg 1988; 123:1459–1464.

19. Winchurch RA, Thepari TN, Munster AM. Endotoxemia in burn patients: levels of circulating endotoxins are related to burn size. Surgery 1987; 102:808–812.
20. Levine GM, Deren JJ, Steiger ET, Zinno R. Role of oral intake in maintenance of gut mass and disaccharide activity. Gastrenterology 1974; 67:975–982.
21. Ford WDA, Boelhauwer RU, King WWK, et al. Total parenteral nutrition inhibits intestinal adaptive hyperplasia in young rats: reversal by feeding. Surgery 1984; 96:527–534.
22. Levine GM, Deren JJ, Yezdimir E. Small bowel resection: oral intake is the stimulus for hyperplasia. Am J Dig Dis 1976; 21:542–546.
23. Petersen SR, Kudsk KA, Carpentier G, Sheldon G. Malnutrition and immunocompetance: increased mortality following an infectious challenge during hyperalimentation. J Trauma 1984; 21: 528–533.
24. Souba WW, Smith RJ, Wilmore DW. Glutamine metabolism by the intestinal tract. JPEN 1985; 9:608–617.
25. Spaeth G, Berg RD, Specian R, Deitch EA. Food without fiber promotes bacterial translocation from the gut. Surgery 1990; 108: 240–247.
26. Steiner M, Bourges HR, Freedman LS, Gray SJ. Effect of starvation on the tissue composition of the small intestine in the rat. Am J Physiol 1968; 215:75–77.
27. Johnson LR, Copeland EM, Dudrick SJ, et al. Structural and hormonal alterations in the gastrointestinal tract of parenterally fed rats. Gastroenterology 1975; 68:1177–1183.
28. Watson LC, Abston S. Prevention of upper gastrointestinal hemorrhage in 582 burned children. Am J Surg 1976; 132:790–793.
29. Choctaw WT, Fujita C, Zawacki BE. Prevention of upper gastrointestinal bleeding in burn patients. Arch Surg 1980; 115:1073–1076.
30. Hillman KM, Riordan T, O'Farrell SM, Tabaqchali S. Colonization of the gastric contents in critically ill patients. Crit Care Med 1982; 10:444–447.
31. DuMoulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonization of the airway. Lancet 1982; i:242–245.
32. Moore FA, Moore EE, Jones TN, et al. TEN versus TPN following major abdominal trauma-reduced septic morbidity. J Trauma 1987; 29:916–923.

# BOOK REVIEWS

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**The Cause and Management of Aneurysms.** R. M. Greenhalgh, J. A. Mannick, and J. T. Powell. 486 pp. Philadelphia: WB Saunders, 1990.

THIS VOLUME, The Cause and *Management of Aneurysms*, is unique because of its international flavor and because it combines the latest knowledge concerning the clinical aspects of aneurysms as well as information from recent advances in the basic sciences related to aneurysms. It is edited by two internationally acclaimed clinical vascular surgeons and a scientist well known for his contributions to basic science related to aneurysm disease.

Appropriately the introduction begins with an excellent, concise, and well-illustrated review of the historical aspects of aneurysm surgery. The section on mechanisms of arterial dilatation contains chapters discussing the relationship of the development of aneurysms to atherosclerotic disease, elastin and collagen metabolism, and the inherited defects that may result in aneurysm formation, including Ehlers-Danlos, Marfan's, and cystic medial necrosis syndromes.

The next section deals with the presentation and clinical evaluation of aneurysms. It covers the controversy regarding the necessity for preoperative angiography as well as material on other imaging modalities, particularly computerized axial tomography and magnetic resonance imaging. The segment on inflammatory aneurysms is particularly valuable because it describes not only the familiar inflammatory aneurysm seen in the United States but also the unique tuberculous and non-tuberculous idiopathic inflammatory arteriopathies seen in Southern Africa and the Orient. The final section, on the management of aneurysms, contains chapters on the management and surgical technique for repair of aneurysms in the common clinical locations. Each of the authors of these chapters is well known for his contributions and predictable prejudices. For example advocates of the retroperitoneal and the midline transabdominal approaches to abdominal aortic aneurysm each claims that his technique is superior with respect to postoperative pain. The controversy regarding what size aneurysm should be subjected to surgical correction is addressed briefly, as is the problem of the management of aneurysms in the very elderly patient.

The printing is of high quality and the reproduction of the many well-chosen black and white illustrations is superior. One of the most valuable aspects of this type of work is the references to original sources. While these are admirably recent, there are a rather large number of errors and references that are incomplete or listed as in press that have not been updated.

This book has much to offer and is recommended to both the mature vascular surgeon and the less experienced student of arterial aneurysms. Its international perspective is unique and one of its strongest points. Few other volumes so completely cover both the clinical and basic science aspects of arterial aneurysms as is found in this book.

RICHARD L. MCCANN, M.D.
Durham, North Carolina

**Surgical Endocrinology: Clinical Syndromes, Second Edition.** Stanley R. Friesen and Norman W. Thompson. 474 pp. Philadelphia: JB Lippincott, 1990. $79.50.

NORMAN THOMPSON joined Stanley R. Friesen as coeditor of this most welcome second edition of a classic endocrine text.

There can be few disciplines where progress has been more rapid on every front than endocrinology. This is reflected in the plethora of new concepts, new humoral substances and syndromes, as well as recent advances in localization and therapeutic options available to the endocrine surgeon.

The historical foreword by Richard Welbourn provides an important background to complexities of modern endocrinology.

The first section covers recent advances in neurotransmitters and the cytochemical identification of endocrine cells. The emphasis thereafter is on the identification of specific syndromes with clinical management firmly integrated into pathophysiology.

The surgeon's perception of the special problems of anesthesia in endocrine surgery is a welcome feature. The diagnostic steps required to obtain the biochemical evidence to establish the diagnosis of a clinical syndrome often are very complex. The diagnostic criteria across the whole range of disorders are logically and clearly presented.

The selection of localization procedures can be confusing. The most relevant and cost-effective methods are identified very clearly. The precision with which a diagnosis can now be made and the accuracy of localization of abnormal endocrine tissue has enabled endocrine surgeons to obtain outstanding results from functionally directed procedures. Endocrine problems that require surgery are relatively rare so that this clear authoritative and practical reference volume with its impressive basic science foundation is most welcome. This book is an invaluable reference text for any surgeon planning to operate on an endocrine gland.

IVAN D. A. JOHNSTON, F.R.C.S., F.A.C.S. (Hon)
Newcastle Upon Tyne, England

**Progress in Hepatic, Biliary, and Pancreatic Surgery.** John S. Najarian and John P. Delaney. 483 pp. St. Louis, MO: Mosby Year Book, 1990.

THIS WORK represents the compilation of the proceedings of a postgraduate course at the University of Minnesota. It provides an important update on what is new and controversial in the management of hepatic, biliary, and pancreatic diseases. As new technologies have been introduced and refined, a multidisciplinary approach has evolved for many of these disorders. The importance of this process is reflected in the diversity of contributors to this work and the inclusion of several chapters that focus on inflammatory diseases of the liver, specifically, hepatitis. These latter chapters are particularly well done and Dame Sheila Sherlock's chapter Viral Hepatitis and The Surgeon is one that all surgeons, regardless of their clinical interests, should read and keep in their library.

The book is appropriately divided into 49 chapters. Many focus on age-old problems that continue to challenge clinicians: liver trauma, acute cholecystitis, bile duct injury, and bleeding esophageal varices. In addition there are a number of chapters that deal with new areas of knowledge, including the use of intraoperative ultrasound for liver and pancreatic surgery, implantable hepatic artery pumps, current use of endoscopic and radiologic techniques for the management of biliary disorders, and the current role of nonoperative methods in the management of patients with gallstone disease. Of particular interest in terms of clinical importance and historical perspective is the chapter The Zollinger–Ellison Syndrome 1989 by Dr. Robert M. Zollinger. In addition to these 49 chapters, there are seven panel discussions that are detailed. These sections have questions that were addressed by the various presenters during the proceedings. Most of the questions are pointed inquiries regarding specific clinical problems and management issues. These are frequently controversial and, as one would anticipate, often there is disagreement among the expert panelists. The 'give and take' is particularly enlightening and one can sense the excitement and controversy that went on during various portions of this meeting. These segments of the book are stimulating and informative and allow the reader the opportunity to witness discussions between noted experts in the areas of hepatic, biliary, and pancreatic surgery.

In general the style of the book provides for easy reading and the illustrations, figures, and tables are legible and add considerably to the text. Drs. Najarian and Delaney have done a masterful job in selecting an outstanding faculty for their proceedings and this is reflected by a book that provides a succinct review of what's new and exciting in hepatobiliary and pancreatic surgery. If there is a shortcoming, it is that the book does not provide a lot of background information for most of the subjects that are discussed. On the other hand, this is not the intent of this work. This book is designed as an update for housestaff, practicing surgeons, and gastroenterologists who are involved in the care of patients with hepatobiliary and pancreatic disease. All in all, this is a well-done, valuable text that provides current information about recent advances in hepatobiliary and pancreatic surgery.

JOEL J. ROSLYN, M.D.
Los Angeles, California

**Techniques in Aesthetic Craniofacial Surgery**. Kenneth E. Salyer. 304 pp. Philadelphia: JB Lippincott, 1989. $137.50.

DR. SALYER COMPREHENSIVELY reviews the state of the art of craniofacial surgery, depicting the imbrication of Dr. Tessier's revolutionary contributions into the mainstream of plastic surgery. His prefatory remarks clearly reflect his personal priorities regarding the indications for operative intervention—that facial aesthetics mandate primary consideration while the traditional emphasis on occlusion is relegated to the subordinate role. Although his philosophy has not yet been embraced widely by plastic surgeons, the public's preoccupation with and demand for procedures that do not enhance function provide adequate testimony to the importance of one's appearance. How else to explain the mercurial rise in the popularity of liposuction such that it is now the most popular plastic surgery procedure supplanting breast augmentation? The body of the book dramatically demonstrates the power of these techniques, while the accompanying documentation of their safety validates their use to this end.

The book bears the imprimatur of a single author whose expertise provides solutions for virtually the entire scope of facial deformities. Dr. Salyer's conversational style flows smoothly, although his stream-of-consciousness approach offers little critique of alternative surgical options. The chapters are arranged anatomically and adhere to the common sequence: introduction, indications, techniques, applications, and complications, thus affording ready access. As befits the emphasis on aesthetics, the results of surgery are beautifully documented with color photographs. The pre- and postoperative views are quite uniform in their tone and attitude, while the legends thoroughly describe the diagnosis, procedure, and duration of follow-up. Many schematic diagrams are juxtaposed closely to the relevant patient photographs and are not only in color but also are line drawings that photocopy well.

The bibliography for each chapter is of adequate scope and although Dr. Salyer generally ascribes various techniques to the surgeons who originated them, there are no footnotes. The only notable failing is the pervasive misspelling of words of foreign origin. Among others, apologies are due to the French for the Westernization of bandeau to bando and to the Romans, who most certainly would have described the pear-shaped nasal aperture as piriform, not pyriform, and to the Australian Wood-Smith, who despite the resemblance of these techniques to cabinetry, is not a woodsmith. This lament not withstanding, it would behoove any surgeon who endeavors to perform these operations to acquire this text and share the vast experience of one of our most progressive craniofacial surgeons.

GREGORY L. RUFF, M.D.
Durham, North Carolina

**Clinical Nutrition: Enteral and Tube Feeding (2nd Edition).** John L. Rombeau and Michael D. Caldwell. 638 pp. Philadelphia: WB Saunders, 1990. $95.00.

THE SECOND EDITION of the text *Clinical Nutrition: Enteral and Tube Feeding,* edited by John L. Rombeau and Michael D. Caldwell, is perhaps the most informative and current text on enteral feeding that is available. The book is practical not only for physicians and surgeons but also for pharmacists and dietitians who participate in the nutritional care of patients. The authors provide an excellent overview of the various types of enteral feedings and the kinds of techniques used to provide enteral nutrition. Nutritional support of patients with various diseases (cancer, trauma, sepsis, liver disease, renal failure, and head injury) are well reviewed by authorities in the field.

The primary slant of the text is a clinical one, but there are several chapters that cover basic science phenomena such as absorption of nutrients and hormone substrate interactions. Although substrate use at the cellular and subcellular levels is covered rather superficially, no doubt future editions of this text will include chapters that summarize our current knowledge of the transport and metabolism of amino acids by the gut mucosal cells as well as by hepatocytes. Such an overview could cover effectively regulation of cell membrane transport as well as look at nutrient regulation of gene expression at the molecular level. An introductory chapter on the importance of enteral nutrition from a general standpoint might also be useful. Such a chapter could review the role of enteral nutrition in maintaining the gut mucosal barrier and include a discussion of gut immune function.

The second edition of this excellent book has built on its predecessor. The editors are to be commended for including recently acquired knowledge as well as addressing some of the medical/legal issues that are involved in feeding certain patients. No doubt future editions of this text will be useful to all individuals who participate in nutritional care of hospitalized patients.

WILEY WILLIAM SOUBA, M.D.
Gainesville, Florida

**Pancreas Transplantation: Experimental and Clinical Studies.** Jean-Paul Squifflet. 188 pp. Basel, Switzerland: Karger, 1990. $98.00.

PANCREATIC TRANSPLANTATION IN humans has evolved numerically from the first reported case by Kelly at the University of Minnesota in 1966 to more than 400 cases each year. Some centers report 95% 1-year patient survival and 90% pancreas and kidney survival rates. The rapid improvement in clinical results during the past 24 years results from a collective experimental and clinical experience that is well summarized in this timely monograph. The main question of this field still remains to be conclusively answered, specifically whether pancreas transplantation can reverse or prevent the secondary complications of diabetes. The author has drawn extensively from his own experience as well as the data base of the International Pancreas Transplant Registry at the University of Minnesota to provide a thorough review of pancreatic, although not islet cell, transplantation.

After a historical introduction to the field, the author includes a 30-page section on experimental studies in pancreas and islet transplantation. Although brief, most important experimental contributions are covered in this chapter. The remaining six chapters of the book cover the clinical aspects of patient selection, donor selection, donor operative technique, recipient operative technique, postoperative management, and a summary of clinical results. The text is amply illustrated by 65 figures and 21 tables and is referenced thoroughly with 481 citations. The current controversies of the field are presented, including duct management technique, whole *versus* segmental grafts, immunosuppression, and patient selection. The discussion of clinical pancreas transplantation is the most up-to-date and complete review available in a single volume. The author is to be congratulated on his personal contributions to the field as well as for providing the best book available on the subject of pancreas transplantation.

STUART J. KNECHTLE, M.D.
Madison, Wisconsin

# LETTERS TO THE EDITOR

May 11, 1990

Dear Editor:

We read with interest the article '100 Consecutive Common Duct Explorations Without Mortality' by Dr. Pappas and colleagues (Ann Surg 1990; 211:260–262). An 85% incidence of negative common bile duct (CBD) exploration is unacceptably high and makes us wonder whether the authors' indications of CBD exploration were justified and valid. In all likelihood, intraoperative cholangiograms were not done routinely before exploration. A selective (if not routine) intraoperative cholangiography would have avoided unnecessary explorations in many cases.

The group undergoing emergency surgery (35%) with a proportional high incidence of complications (9 of 15 cases) is undefined in the data.

Retained stones were managed successfully with endoscopic extraction. The high success rate (80% to 90%) and low morbidity (about 10%) and mortality (less than 1%) rates of endoscopic methods of extraction of CBD stones, especially in the high-risk patient group with associated comorbid conditions, should make it a favored method of treatment in most cases. The indications of surgical exploration of CBD should become more stringent through nonavailability or failure of endoscopic treatment and not weak, as used by the authors.

S. S. SIKORA
V. K. KAPOOR
Lucknow, India

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June 19, 1990

Dear Editor:

Drs. Sikora and Kapoor commented on the high incidence of negative common duct exploration in our paper '100 Consecutive Common Duct Explorations without Mortality' (Ann Surg 1990; 211:260–262). As we noted in the manuscript, in reading the medical records of these patients, it was apparent that common duct stones were encountered several times and pushed to the duodenum without actually removing the stones. It is difficult to quantitate the exact number of stones that were found because the ones pushed through to the duodenum were not sent for pathologic examination. Even accounting for this, our incidence of finding stones during common duct exploration is smaller than in other published studies. We noted this in the discussion and suggested that this is one possible reason for our low rates of morbidity and mortality with these cases.

Drs. Sikora and Kapoor are correct that intraoperative cholangiograms were not done routinely on every case before exploration. It is also true that some of these explorations may have been avoided with a normal cholangiogram. Drs. Sikora and Kapoor also commented on the fact that some of our patients underwent emergency surgery. These are patients who had cholecystectomy and common duct exploration on the same day that the diagnosis was made, in contrast to those in which the surgeon thought that the operation could wait until the following day or the following week. The incidence of complications in this group of patients is consistent with that reported in the literature. Concerning the success of endoscopic extraction of gallstones quoted in Drs. Sikora and Kapoora's letter (80% to 90%), this is certainly the number that is quoted in the medical literature by major medical centers with large series of patients. Whether this is the success rate in the community has not been adequately documented. In addition the morbidity rate of 10% and the mortality rate of less than 1% with endoscopic extraction of common duct stones needs to be added to the risk of cholecystectomy if both procedures are to be done on each patient. While we agree that high-risk patients should undergo endoscopic retrograde cholangiopancreatography before cholecystectomy in an effort to avoid common duct exploration, this is certainly not true for the routine patient. For the low-risk patient, we continue to recommend exploratory laparotomy, cholecystectomy, and common duct exploration for the treatment of common duct stones. Whether laparoscopic cholecystectomy changes these recommendations has not been determined.

THEODORE N. PAPPAS, M.D.
DAVID C. BROOKS, M.D.
Durham, North Carolina and Boston, Massachusetts

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16 July, 1990

Dear Editor:

I have just read the article 'Preoperative Chemotherapy for Soft-tissue Sarcomas of the Extremities' (Ann Surg 1990; 211: 476–481). This information is potentially very exciting and could provoke significant change in the management of patients with large, high-grade, extremity soft-tissue sarcomas.

I would like some additional information and would request that the authors address these issues. First and most important is the relationship between the size of the tumor and the response of chemotherapy. I do not find in the article mention of a relationship between size of tumor and response. The tumors range from just more than 5 cm to 24 cm in diameter. Our data would suggest that although soft-tissue lesions larger than 5 cm had a worse prognosis than those less than 5 cm, there is a progressive increase in the mortality rate related to size, particularly for those lesions that are histologically high grade and larger than 10 cm in diameter. If the small lesions responded more to the preoperative chemotherapy than the large lesions, this could account for at least some of the difference in the disease-free survival rate between the responders and nonresponders.

Second I assume that response is only a clinical evaluation of size because some of these patients received preoperative irradiation to the tumors and therefore the histologic response could not be measured. It is unfortunate that these treated tumors were not excised before irradiation.

Finally one wonders if there is any relationship between survival rate and the use of pre- and postoperative irradiation compared to postoperative irradiation alone.

DEMPSEY S. SPRINGFIELD, M.D.
Boston, Massachusetts

July 26, 1990

Dear Editor:

I appreciate the comments of Dr. Springfield. He raises three questions to which I will respond.

The first issue is whether there is a relationship between the size of an extremity sarcoma and the response to neoadjuvant chemotherapy. Careful re-examination of our data did not demonstrate any such correlation. All of the tumors in our series were larger than 5 cm in largest diameter, and most ranged in size between 10 and 15 cm. By the parameters of response measured (*i.e.*, radiologic criteria, clinical examination, or histopathologic response), there was no correlation between size of tumor and degree of response.

Second response was assessed either clinically, radiologically, or pathologically. Some patients did receive preoperative radiotherapy and this was necessitated by the size of the tumor vis-á-vis critical neurovascular and osseous structures. I agree that for research purposes it is unfortunate that these treated tumors were not excised before irradiation. However, as a practical matter, these tumors were managed with radiation before excision to salvage the limb.

Third we did not discern any relationship between survival and the use of pre- and postoperative radiation compared to postoperative radiotherapy alone. As is well known, preoperative radiation can be delivered through smaller operative fields, but with the subsequent risk of severe wound complications in 20% to 30% of the patients. Postoperative radiation, of necessity, requires a larger radiotherapy field to encompass the entire surgical arena. In addition postoperative radiotherapy may not be as efficacious in those patients for whom anticipated close margin problems have been identified on the basis of preoperative assessment.

I hope this information is valuable to you.

RAPHAEL E. POLLOCK, M.D., PH.D., F.A.C.S.
Houston, Texas

# Somatostatin and the Treatment of Cancer

In 1955 the surgical treatment of gastrointestinal diseases changed with the description of the Zollinger–Ellison syndrome.[1] For the first time a common disorder, peptic ulcer disease, was linked to a peptide-producing tumor. This ushered in an entire generation of surgeons and physicians attempting to diagnose and treat diseases caused by humoral abnormalities. In addition, scientists began investigating other common gastrointestinal diseases for an endocrine basis, eventually leading to the description of much of our current knowledge of gastric and pancreatic function. With the introduction of a somatostatin analogue, octreotide, the evolution of the management of gastrointestinal disease has again entered a new phase. Preliminary clinical use of octreotide suggests that peptide manipulation can be used to influence a wide variety of surgical diseases.[2,3]

Evers and associates from the University of Texas at Galveston have reviewed the use of somatostatin and its analogues in the treatment of cancer. The suggestion that the inhibition of growth factors or growth receptors may influence tumor growth is the basis for the use of octreotide in these patients. It is clear that growth factors probably drive the rapid growth of most malignancies and discovery of growth factors and their receptors certainly holds the key to the biologic or physiologic management of neoplasia. As reviewed by Evers and associates, somatostatin's impact on the growth of tumors may occur by direct inhibition of growth receptors on the tumor, inhibition of the release of growth factors that influence tumor growth, or by the inhibition of the release of other hormones that augment tumor growth. Unfortunately this field can at best be described as being in its infancy because tumor responses to somatostatin and its analogues are available only in animal experiments and in very limited clinical settings. The malignancies discussed include carcinoma of the breast, lung, pancreas, prostate, and a variety of endocrine tumors. Although most of the clinical data currently available have been presented as anecdotes, certainly several of these cases generate excitement because the tumor responses to somatostatin and its analogues have been dramatic.

Physiologic manipulation of tumors predictably will bring surgical oncology into a new era. Specifically peptide manipulation of tumors as reviewed in this manuscript may represent genuine progress in the battle against malignancies.

THEODORE N. PAPPAS, M.D.
Durham, North Carolina

## References

1. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumor of the pancreas. Ann Surg 1955; 142:709–728.
2. Mulvihill SJ, Pappas TN, Passaro E Jr, Debas HT. The use of somatostatin and its analogs in the treatment of surgical disorders. Surgery 1986; 100(3):467–475.
3. Geoghegan JG, Meyers WC, Pappas TN. Octreotide: clinical experience in 62 patients with gastrointestinal disease. Gastroenterology 1990; 98(5):A47.

# Somatostatin and Analogues in the Treatment of Cancer

## *A Review*

B. MARK EVERS, M.D., DILIPKUMAR PAREKH, M.D., COURTNEY M. TOWNSEND, JR., M.D.,
and JAMES C. THOMPSON, M.D.

*From the Department of Surgery, University of Texas Medical Branch, Galveston, Texas*

**Somatostatin is a naturally occurring cyclic tetradecapeptide that inhibits release of growth hormone and all gastrointestinal hormones. The beneficial effect of somatostatin in the treatment of certain hypersecretory disorders of hormone excess is well recognized; however its clinical usefulness has been limited in the past by its extremely short plasma half-life. The development of long-acting somatostatin analogues has provided clinically useful agents for treatment of hormone-producing tumors. In addition to well-known inhibiting effects on hormone release and actions, recent studies using experimental tumor models have demonstrated an antiproliferative effect of somatostatin and its analogues on growth of a variety of neoplasms. The exact role of somatostatin analogues in cancer therapy has yet to be established; however studies suggest that these agents could provide a useful and relatively nontoxic adjuvant therapy in the treatment of certain tumors. In this review, the oncologic application of somatostatin and possible mechanism of action are examined and current clinical and experimental studies are summarized.**

SOMATOSTATIN WAS ISOLATED and characterized by investigators working in the laboratory of Guillemin at the Salk Institute[1] in 1973 following the original observations made by Krulich and coworkers[2] during a search for a growth hormone-releasing factor. Since the identification and purification of somatostatin-14 (Fig. 1), precursor forms of greater molecular weight have been recognized.[3-5] Somatostatin-28, or prosomatostatin, is a 28-amino acid polypeptide with somatostatin-14 making up the C-terminus[3] (Fig. 2). Preprosomatostatins are even larger precursor forms of 120 or more amino acids, with somatostatin-28 located at the C-terminus.[4] All of these forms exert biologic activity but differ in their relative potency.[6]

Somatostatin has been identified by a variety of immunocytochemical and radioimmunoassay techniques in multiple sites throughout the nervous system, including the cerebral cortex, cerebellum, hypothalamus, pituitary infundibular process, pineal gland, and spinal cord.[4,7] In the gastrointestinal tract, somatostatin has been found in the stomach (antrum, body, and fundus), the duodenum, jejunum, ileum, colon, and pancreas; the greatest amount is present in the stomach and pancreas.[3,4,7] More than 90% of the somatostatin immunoreactivity in the human gut is present within mucosal endocrine cells called D cells.[4,8] Muscle-layer somatostatin is located in nerves of the myenteric plexus.[4] Somatostatin in the pancreas is located in the D cells at the periphery of the islets of Langerhans.[4]

Somatostatin is characterized as a regulatory-inhibitory peptide with exocrine, endocrine, paracrine, and autocrine activity.[4] The general inhibitory function of somatostatin is wide ranging and affects a number of organ systems. Many have characterized it as the universal endocrine off-switch. Somatostatin inhibits the release of growth hormone and somatomedin C and all known gastrointestinal hormones.[3-8] Somatostatin also inhibits gastric acid secretion and motility, intestinal absorption, pancreatic bicarbonate and enzyme secretion, and selectively decreases splanchnic and portal blood flow in dogs and humans without affecting mucosal blood flow.[3-10]

Several clinical trials demonstrated impressive efficacy of somatostatin and its analogues in a variety of hypersecretory disorders resistant to standard therapy, including

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Dr. Parekh is a Visiting Scientist from the University of Witwatersrand, Johannesburg South Africa and is supported by a scholarship from the Medical Research Council and Michael and Janie Miller Foundation.

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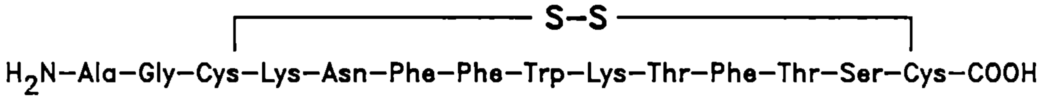

S–S
H₂N–Ala–Gly–Cys–Lys–Asn–Phe–Phe–Trp–Lys–Thr–Phe–Thr–Ser–Cys–COOH

FIG. 1. Amino acid sequence of somatostatin-14.

acromegaly,[11,12] pancreatic ascites,[13] and pancreatic cholera.[14] They also proved useful in symptomatic treatment of gastrointestinal neoplasms of endocrine origin, including Zollinger–Ellison syndrome,[15–18] insulinoma,[19,20] VIPoma (tumors resulting from hypersecretion of vasoactive intestinal peptide),[21–24] glucagonoma,[25,26] and carcinoid tumors.[17,27,28] Intriguing additions to the reported success of somatostatin in relieving symptoms produced by endocrine tumors have been reports of antiproliferative actions of somatostatin (both *in vivo* and *in vitro*) on various solid tumors, including breast,[29–33] prostate,[29,34–37] colon,[38–40] pancreatic,[6,29,41–43] and small cell lung carcinoma.[44,45]

The exact mechanism of the antitumor effect of somatostatin is not known, but some possibilities include one (or a combination) of the following: (1) a direct antiproliferative effect mediated through specific, high-affinity somatostatin receptors; (2) inhibition of secretion of gastrointestinal hormones thought to be important in tumor growth (that is, gastrin, secretin, cholecystokinin [CCK], and insulin); and (3) inhibition of release of growth hormone and other growth factors (that is, epidermal growth factor [EGF] and somatomedin C [IGF-I]).

Mascardo and Sherline[46] demonstrated direct antiproliferative effects of somatostatin by noting *in vitro* inhibition of EGF-induced DNA synthesis and cell replication by blocking centrosomal separation in gerbil fibroma and HeLa cells. Direct effects of somatostatin may be mediated through its interaction with specific somatostatin receptors found on normal cells and on cancer cells. Hierowski and colleagues[43] found that binding of somatostatin to its membrane receptors located on the pancreatic cancer cell line MIA PaCa-2 activates dephosphorylation of the EGF receptor, which prevents EGF-induced growth.

The clinical usefulness of native somatostatin is limited greatly by its short plasma half-life (1 to 3 minutes in humans).[6] Somatostatin analogues were developed that are long-acting and more potent than native somatostatin-14. The first such analogue was SMS 201–995 (SANDOSTATIN® [octreotide acetate]) (Fig. 3). SMS 201–995 is a synthetic octapeptide with a prolonged circulating half-life of approximately 41 to 58 minutes in humans when administered intravenously.[6] The elimination half-life of SMS 201–995, when given subcutaneously, is even longer (approximately 113 minutes in healthy volunteers).[47–49] This analogue was found to be three times more potent than native somatostatin in suppressing glucose-stimulated insulin secretion and 19-times more potent than native somatostatin in inhibiting growth hormone secretion.[48] In recent years, major strides were made in the synthesis of newer, longer-acting analogues specifically designed for antitumor activity. Schally[29] and Cai and coworkers[50] synthesized more than 300 analogues using solid-phase methods. These octapeptide ‘superanalogues’ are more potent and have longer durations of action than either native somatostatin or SMS 201–995.

The somatostatin analogues have a wide therapeutic index and seem to be free of major side effects.[29,48,51] Most of the reported side effects are gastrointestinal in nature and include minor nausea, bloating, diarrhea, constipation, or steatorrhea. Currently SMS 201–995 is approved only for the control of symptoms associated with metastatic carcinoid or VIP-secreting tumors; however use of these analogues may prove beneficial in the future as novel adjuvant agents in cancer chemotherapy. The success of somatostatin in treating the hypersecretory disorders of patients with endocrine tumors has been documented extensively in many clinical trials.[13–22] This review will focus specifically on the oncologic application of somatostatin and its analogues in the treatment of endocrine and nonendocrine solid tumors.

## Breast Cancer

Immunoreactive somatostatin-14 is found in human breast milk in a concentration 10 times higher than in plasma.[52] Somatostatin in milk possesses bioactivity as demonstrated by its ability to inhibit basal- and prostaglandin-induced release of growth hormone from anterior pituitary cell cultures in a fashion that is parallel to that of synthetic somatostatin-14.[52] Somatostatin activity also was demonstrated in human breast cancers. Using receptor autoradiography, Reubi and coworkers[53] demonstrated the presence of high-affinity somatostatin receptors in 3 of 39 breast cancers. The presence of somatostatin recep-

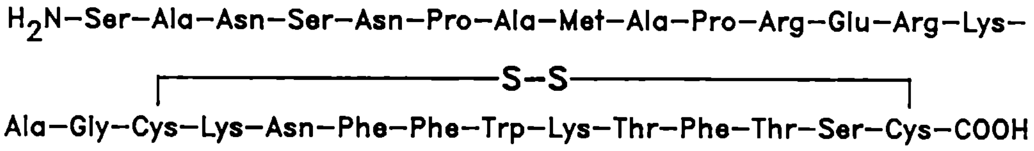
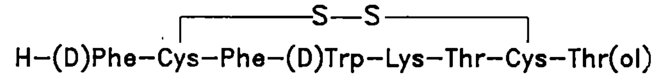

H₂N–Ser–Ala–Asn–Ser–Asn–Pro–Ala–Met–Ala–Pro–Arg–Glu–Arg–Lys–
S–S
Ala–Gly–Cys–Lys–Asn–Phe–Phe–Trp–Lys–Thr–Phe–Thr–Ser–Cys–COOH

FIG. 2. Amino acid sequence of somatostatin-28.



$$\text{H–(D)Phe–}\overbrace{\text{Cys–Phe–(D)Trp–Lys–Thr–Cys}}^{\text{S—S}}\text{–Thr(ol)}$$

FIG. 3. Amino acid sequence of long-acting somatostatin octapeptide analogue (SMS 201-995).

tors did not correlate with the age of the patient or with the number of estrogen and progesterone receptors. Spring-Mills and colleagues[54] demonstrated somatostatinlike immunoreactivity in a majority of human breast cancers studied. These findings of somatostatinlike activity in breast milk and specific high-affinity somatostatin receptors in human breast tissue led several investigators[31,33] to speculate that the role of somatostatin may be that of an autocrine or paracrine factor linked to control of breast cell proliferation.

Scambia and coworkers[33] studied *in vitro* effects of somatostatin-14 and the long-acting somatostatin analogue, SMS 201–995, on three human breast cancer cell lines (CG5, T 47 D, and ZR 75-1). They found a dose-dependent inhibition of growth of all three lines with either native somatostatin-14 or SMS 201–995. Significant inhibition was noted in CG5 cell growth at a concentration of 0.01 nmol/L (nanomolar) of SMS 201–995. Maximal inhibition (40%) occurred with a concentration of 100 nmol/L. The effects were less pronounced with T 47 D and ZR75-1. A significant inhibition in growth (approximately 10% compared to untreated control cells) was not noted until a concentration of 10 nmol/L of somatostatin was used. Further increases in the concentration of somatostatin failed to produce additional inhibition. Although not mentioned in their studies (and not specifically measured), one possible explanation for the increased inhibitory effect of somatostatin on CG5 compared to T 47 D and ZR75-1 may be the presence of somatostatin receptors. CG5 is a variant of another breast cancer cell line, MCF-7, which has a single class of high-affinity somatostatin receptors. Using the MCF-7 cell line, Setyono-Han and colleagues[31] studied *in vitro* antiproliferative effects of somatostatin-14, somatostatin analogue, SMS 201–995, and another long-acting somatostatin analogue, CGP 15–425. All three agents inhibited growth of MCF-7 with maximal inhibition of cell proliferation noted at a concentration of 10 nmol/L (approximately 75% inhibition). These two studies suggest a direct inhibitory effect of somatostatin on breast tumor cells.

Several *in vivo* investigations corroborated the *in vitro* findings of somatostatin-induced inhibition of breast cancer. Rose and coworkers[30] studied the effects of somatostatin-14 and a long-acting somatostatin analogue, L 362,823, on the growth of mammary carcinomas induced by N-nitrosomethylurea in female rats. Pergolide, an agent that suppresses serum prolactin, had no effect on tumor growth, but when it was combined with a 7-day treatment of somatostatin-14 (20 μg/hour *via* osmotic minipump), tumor surface areas decreased significantly. Once somatostatin treatment was stopped, the tumors underwent regrowth despite the continuation of pergolide. Similar findings were noted when the experiment was repeated using the long-acting somatostatin analogue, L 362,823 (5 μg/hour *via* osmotic minipump). Neither pergolide nor L 362,823 were effective as single agents. When L 362,823 was administered for 7 days in combination with pergolide, tumor regression again was noted. With cessation of L 362,823, however, immediate tumor regrowth was found. These findings suggest a cytostatic effect of somatostatin on this chemically induced mammary carcinoma.

In another model of chemically induced rat mammary cancer, Klijn and colleagues[55] studied the effects of different dosages (0, 0.05, 0.2, 1.0, 5.0, and 20 μg) of somatostatin analogue SMS 201–995 administered twice daily for 3 weeks to rats with dimethylbenzanthracene-induced tumors. They found a similar bell-shaped dose-response curve as noted in *in vitro* studies from their laboratory.[31] Maximal tumor inhibition (83%) was noted with SMS 201–995 (0.2 μg, twice daily).

Weber and coworkers[32] recently reported on the effect of SMS 201–995 on the growth of estrogen-dependent (MCF-7) and estrogen-independent (BT-20) human breast cancer that was xenografted in nude mice. SMS 201–995 (4 μg, twice daily) significantly decreased MCF-7 tumor volume and prolonged tumor doubling time compared to controls. A much higher dosage of SMS 201–995 (50 μg, twice daily) was required to produce a modest, but significant, prolongation of BT-20 tumor doubling time and a decrease in the calculated growth increment. The volume of the BT-20 tumor was not affected by SMS 201–995.

The mechanism by which somatostatin inhibits growth of breast cancer in experimental studies is not known. *In vitro* studies demonstrate a direct effect of somatostatin possibly mediated through specific somatostatin receptors.[31,33] Also somatostatin may act indirectly by inhibiting release of growth factors known to stimulate human breast cancer cells. EGF and IGF-I stimulate growth of breast cancer *in vitro*, and several breast cancer lines, including MCF-7, have specific receptors for EGF or IGF-I.[22,56] Somatostatin and its analogues reduce levels of these growth factors, which may contribute to the antiproliferative effect seen in experimental studies.

## Lung Cancer

Human small cell lung cancer accounts for 20% to 25% of all lung cancer.[57] It is a rapidly growing tumor characterized by early metastasis and ectopic hormone production.[58,59] Advances in multidrug chemotherapeutic regimens modestly improved survival, but the prognosis is still dismal.[60] Taylor and colleagues[45] demonstrated somatostatin receptors on human small cell lung cancer cells, a finding that provides a possible clue for a growth-regulatory function for somatostatin. To test this hypothesis, a somatostatin analogue, BIM-23014 C, was used to treat the human small cell lung cancer cell line, NCI-H69.[45] *In vitro* studies demonstrated inhibition of tumor cell proliferation (59% of untreated controls) with a concentration of 10 nmol/L of BIM-23014 C. *In vivo* growth was assessed by injecting NCI-H69 cell suspension subcutaneously into the flanks of nude mice. Treatment was initiated with BIM-23014 C (500 $\mu$g/injection, twice daily) administered intraperitoneally in one group, subcutaneously around the tumor in a second group, and in a remote subcutaneous location in a third group. The mean tumor lag time was delayed in mice treated by intraperitoneal and remote subcutaneous injections, but inhibition of tumor growth at 48 days was dramatic with subcutaneous administration around the tumor. Discontinuing treatment by any route resulted in an acceleration of tumor growth that was similar to the findings of Rose and coworkers[50] in breast cancer. These results would certainly suggest a direct cytostatic effect of somatostatin on NCI-H69 tumor growth, rather than a cytotoxic effect. Consideration must be given also to an indirect effect of somatostatin on tumor growth.

Cuttitta and colleagues,[61] Moody and coworkers,[62] and others[63–66] demonstrated bombesinlike immunoreactivity and a high density of bombesin-binding sites in a number of cell lines of human small cell lung cancer, as well as in resected surgical specimens of tumor. These findings suggest that bombesin may function as an autocrine growth factor. We showed stimulation of growth of NCI-H69 xenografts in nude mice that were treated with bombesin.[67] Somatostatin inhibits the release of bombesin and could affect tumor growth indirectly by this mechanism. Milhoan and colleagues,[44] working in our laboratory, examined the effect of another long-acting somatostatin analogue, MK-678, on NCI-H69 growing in nude mice. Treatment with MK-678 (300 $\mu$g/kg, three times daily) for 46 days resulted in a significant decrease in tumor area (51%), DNA content (64%), and RNA content (55%), as compared to control values. Tumor protein and weight were not significantly reduced. Although the degree of tumor inhibition varies between studies, the data of Milhoan and coworkers[44] and Taylor and colleagues,[45] showing inhibition of NCI-H69 with different somatostatin analogues, suggest a possible role for these agents in the adjuvant therapy for human small cell lung cancer.

## Colon Cancer

Three experimental studies examined the effect of somatostatin on growth of colon cancers.[39,68,69] Certain colon cancers have gastrin receptors and studies using established tumor models demonstrated stimulation of tumor growth by gastrin or its analogues.[68,69] In our laboratory, Singh and coworkers[39] showed that SMS 201–995 inhibited pentagastrin-induced growth of MC-26, a murine colon cancer that is positive for gastrin receptors. Also from our laboratory, Milhoan and colleagues[40] demonstrated significant growth inhibition of two human colon cancers (RIP and DRUM) xenografted in nude mice by the long-acting somatostatin analogue, MK-678 (300 $\mu$g/kg, administered three times daily intraperitoneally), and by $\alpha$-difluoromethylornithine. Alpha-difluoromethylornithine is an irreversible inhibitor of ornithine decarboxylase that catalyzes the first and rate-limiting step in polyamine biosynthesis. Polyamines are essential for cell growth and differentiation and levels are elevated in rapidly dividing tissues. The addition of $\alpha$-difluoromethylornithine to the MK-678 analogue inhibited growth of both RIP and DRUM tumors to a greater extent than either agent alone, a finding that suggests different mechanisms of action.

Smith and Solomon[38] studied cell lines from three human colon cancers (CXI, X56, and HT29). The growth of these tumors *in vivo* was examined in nude mice using X56 and CXI. Three dosages of somatostatin-14 (33, 100, and 300 $\mu$g/kg) were injected subcutaneously twice daily. The growth of X56 was not affected by any dosage of somatostatin. Somatostatin-14 (100 and 300 $\mu$g/kg) significantly reduced tumor volume, weight, protein, and DNA content of CXI after 20 days of treatment. The experiment was repeated using a tumor load of CXI that was five times larger. Somatostatin (100 $\mu$g/kg) decreased the final tumor volume and DNA content only, whereas somatostatin (300 $\mu$g/kg) significantly decreased all measurements of growth.

This study and the previous study by Milhoan and coworkers[40] demonstrate the variable effects of somatostatin-14 and a long-acting analogue, MK-678, on growth of human colon cancer. Three of the four colon cancers were inhibited by administration of somatostatin. Again the exact mechanism for this action cannot be determined specifically. We speculated that a possible mechanism may be an indirect effect on gastrin release or a modulation of gastrin receptors that are present on the colon cancers. As previously noted, Singh and colleagues[39] demonstrated that administration of SMS 201–995 blocked pentagastrin-induced stimulation of MC-26 colon cancer. Gastrin receptors were found to be down regulated in tumors after treatment with somatostatin, which suggests that tumors were made less responsive to the trophic effect of pentagastrin. Smith and Solomon[38] found that pentagastrin (1000 μg/kg) increased the protein and DNA content of the X56 tumor and stimulated all measurements of CXI growth (tumor volume, weight, and DNA and protein content). Although somatostatin was not combined with pentagastrin treatment in the *in vivo* studies, another human colon cancer (HT29) was studied *in vitro*. Gastrin-17 (400 pmol/L [picomolar]) significantly stimulated HT29 cell proliferation and somatostatin-14 (400 pmol/L) decreased cell proliferation. Somatostatin, when combined with gastrin, inhibited the gastrin-induced proliferation of cells (34% reduction in cell counts), compared to the HT29 tumor that was treated with gastrin alone.

### Exocrine Pancreatic Cancer

Adenocarcinoma of the pancreas is common and fatal; it has an overall 5-year survival rate of 1% to 2% and a median survival time of 2.5 months.[29] The only effective treatment is surgical resection, which is possible only in the infrequent case of localized tumor. Radiotherapy and chemotherapy offer no real advantages.[29]

Experimental studies showed an antiproliferative effect of somatostatin and its analogues on the growth of pancreatic cancer. Redding and Schally[41] reported a significant reduction in tumor weight (51%) and volume (67%) in Wistar/Lewis rats bearing the acinar pancreatic tumor DNCP-322 after a 21-day administration of somatostatin analogue [L-5-Br-Trp$^8$] somatostatin-14 (30 μg, twice daily). In the second experiment, Syrian golden hamsters bearing a ductal adenocarcinoma were treated with [L-5-Br-Trp$^7$]somatostatin-14 (20 μg, twice daily) for 30 days with resultant diminished tumor weight and significantly decreased tumor volume compared to controls.

Upp and coworkers[42] in our laboratory demonstrated inhibition of two human pancreatic cancers (SKI and CAV) maintained as nude mouse xenografts by the administration of somatostatin analogue SMS 201–995 (100 μg/kg, IP, three times daily). SKI, a CCK receptor-positive tumor whose growth was stimulated by caerulein[70] and CAV, a CCK-receptor-negative tumor whose growth was not stimulated, both were inhibited to a similar degree by SMS 201–995. Tumor growth of SKI and CAV also was inhibited when treatment was delayed 21 days after tumor implantation.

The exact role that gastrointestinal hormones play in the growth of pancreatic cancer is not known. Townsend and colleagues[71] found that growth of the hamster pancreatic cancer, H2T, was stimulated significantly by administration of caerulein, a CCK analogue, in combination with secretin. As noted above, we also showed significant growth stimulation with caerulein of a human pancreatic cancer (SKI) that has CCK receptors.[70] The inhibitory effect of somatostatin on pancreatic cancer may be due partially to its ability to inhibit the release or action of CCK and secretin. This response could explain the effect seen in SKI but would not explain the inhibition seen in CAV, which does not possess CCK receptors and is not affected by exogenous caerulein.[70]

Other factors (*e.g.*, EGF) may be important in growth of pancreatic cancer. *In vitro* studies by Hierowski and coworkers[43] and Liebow and colleagues[72] demonstrated receptors for somatostatin and EGF in a cell line from an undifferentiated human pancreatic cancer (MIA PaCa-2). Epidermal growth factor stimulates *in vitro* growth of this cancer. Somatostatin reverses the stimulatory effect of EGF by activating dephosphorylation of the EGF receptor.

### Prostate Cancer

The endocrine treatment for advanced prostatic cancer is well established and is based on androgen dependence.[34] Investigators studied the effect of two long-acting somatostatin analogues (RC-160 and RC-121), combined with a luteinizing hormone-releasing hormone agonist ([D-Trp$^6$]-LH-RH), on the growth of the hormone-dependent prostatic cancer, Dunning R-3327H.[35] [D-Trp$^6$]-LH-RH, when given alone, suppressed pituitary and gonadal function and inhibited growth of Dunning R-3327H tumor. The combination of [D-Trp$^6$]-LH-RH and a long-acting somatostatin analogue (RC-121 or RC-160) was more effective in inhibiting tumor growth than either agent alone. A possible explanation suggested by the authors for the enhanced effect seen with combination treatment is that the somatostatin analogues inhibit release of growth hormone and prolactin, which are thought to be important for growth of the normal prostate and possibly play a role in proliferation of malignant cells. Whatever the mechanism, this study suggests that inhibition of hormonally sensitive prostatic cancers may be enhanced with the combination of somatostatin analogues.

### Endocrine Tumors

Somatostatin analogues demonstrated impressive efficacy in the control of symptoms from hormone excess produced by endocrine tumors resistant to standard therapies. Somatostatin has been used in the treatment of the Zollinger–Ellison syndrome of glucagonoma, of VIPoma, of insulinoma, and of carcinoid tumors. The role of somatostatin in the symptomatic treatment of endocrine tumors recently was reviewed extensively.[73–76]

Recent experimental and anecdotal clinical reports suggest that somatostatin may inhibit the growth of endocrine tumors. Experimental *in vivo* studies have been reported for a rat pituitary tumor, 7315a,[77] hamster insulinoma,[20] and a small cell lung cancer.[45] We also studied the effects of SMS 201–995 in small cell lung cancer[44] and in BON, a human carcinoid tumor growing in nude mice.[78]

Lamberts and colleagues[77] studied the effect of the somatostatin analogue, SMS 201–995, on a transplantable prolactin and ACTH-secreting rat pituitary tumor, 7315a. Rats were injected twice daily with SMS 201–995 (2 or 20 μg/kg) for 30 days. Administration of both doses of the somatostatin analogue significantly decreased tumor area and weight. Reubi[20] reported the effects of SMS 201–995 (200 μg/kg/day for 36 days) on a transplantable hamster insulinoma with high-affinity somatostatin receptors. There was a 50% reduction in tumor volume and 40% reduction in tumor weight compared to control animals. In a second experiment, the effects of SMS 201–995 on the growth of an established insulinoma was studied. After 16 days of tumor growth, hamsters bearing the insulinoma tumor were treated with SMS 201–995 (2 or 25 μg/kg/day). Treatment caused a reduction in tumor volume of 33% at the lower dose and of 52% at the higher dose. These findings suggest that the antiproliferative effect of somatostatin was mediated through its receptor.

We examined the effect of somatostatin on a transplantable human carcinoid, BON, that was established in nude mice.[78,79] In the first study, we treated 12 male mice bearing BON xenografts with either SMS 201–995 (300 μg/kg) or saline. At the end of 6 weeks, the tumors were excised and weighed and plasma serotonin was measured. SMS 201–995 significantly reduced plasma serotonin levels and inhibited the growth of BON. In the second experiment, the effect of SMS 201–995 (300 μg/kg) and SMS 201–995 combined with α-difluoromethylornithine (2% in drinking water) was examined on the growth of BON. Both SMS 201–995 and α-difluoromethylornithine inhibited the growth of BON, and the combination of the two inhibited BON to a greater extent than either agent alone. This finding suggests that somatostatin may play a useful role in multiagent chemotherapy.

These studies clearly demonstrate that somatostatin analogue, in a widely ranging dosage (2 μg/kg to 300 μg/kg), inhibits the growth of transplantable endocrine tumors in experimental tumor models. The mechanism of somatostatin's antiproliferative action has not been clarified. Somatostatin may modulate tumor growth by a direct action on somatostatin receptors as demonstrated by Reubi[20] or by an inhibition of release of endogenous hormones that modulate tumor growth in hormone-responsive cancers. Both of these actions (that is, suppression of hormone release and direct suppression of tumor growth) may interact to produce the total antiproliferative effect of somatostatin. Further studies will be needed to clarify the mode of action of the antiproliferative effect of somatostatin in endocrine tumors.

While the experimental studies reviewed above suggest an antiproliferative action of somatostatin, its effects in patients have been variable. Somatostatin analogues were used primarily for symptomatic control in patients with advanced tumors (the majority with extensive liver metastasis). The reported effects of somatostatin on tumor often are based on small experience and usually rely on serial computed tomography or liver scans (Table 1). In-

TABLE 1. *Summary of Antiproliferative Effects of Somatostatin Analogue, SMS 201-995, on Endocrine Tumors in Clinical Studies*

| Investigators | Tumor* | Dosages of SMS 201-995 Duration of Treatment | Effect on Tumor |
|---|---|---|---|
| Shepherd and Senator[80] | Gastrinoma (1) | 1 year | Initial shrinkage of tumor |
| Kvols et al.[28] | Malignant carcinoid (13) | 150 μg tid, 18 months | Apparent shrinkage of hepatic metastasis in 3 patients |
| Souquet et al.[17] | Gastrinoma (2) carcinoid (1) | 100 μg bid, 8 months | Tumor progression |
| Kraenzlin et al.[23] | VIPoma (1) | 50 μg bid, 14 months | Shrinkage of hepatic metastasis |
| Juby et al.[22] | VIPoma (1) | 50 μg bid, 24 months | Tumor size stable during treatment period |
| Clements and Elias[24] | VIPoma (1) | 50 μg daily, 9 months | Shrinkage of hepatic metastasis |
| Altimari et al.[26] | Glucogonoma (1) | 50 μg bid, 8 months | No effect |
| Boden et al.[25] | Glucagonoma (1) | 50 μg bid, 8 months | No effect |
| Williams et al.[49] | VIPoma (4) gastrinoma and/or glucagonoma (6) carcinoid (1) | 50 μg bid, 18 to 38 months | Tumor progression |
| Wiedenmann et al.[81] | Carcinoid (1) | 100 μg bid, 7 months | Shrinkage of hepatic metastasis |

* Number of patients in parentheses.

terpretation of an antiproliferative effect is complicated further in some studies by multiple therapeutic sallies, including chemotherapy and embolization of the hepatic artery. The reported effects of somatostatin analogues on inhibition of tumor growth have been modest or absent. Kraenzlin and colleagues[23] first reported that SMS 201-995 produced shrinkage of a hepatic metastasis in a patient with a VIPoma. In a later study with a long-term follow-up in four patients with VIPomas, Williams and colleagues[49] could not demonstrate a tumor suppression with somatostatin. Studying the effects of various chemotherapeutic regimens in patients with endocrine tumors is further complicated by the fact that these tumors are relatively rare and tumor growth is usually slow, indolent, and unpredictable. Endocrine tumors are infrequent, and this makes the successful evaluation of the role of somatostatin analogues extraordinarily difficult. However consideration of such a study is warranted in solid, nonendocrine tumors, such as pancreatic or breast cancer.

## Conclusions

Somatostatin analogues represent a novel approach from traditional chemotherapeutic regimens in the treatment of certain cancers. The obvious advantages of somatostatin treatment include a wide range of inhibitory and antiproliferative actions with few side effects. The exact mechanism of somatostatin's antitumor effect is unknown. It may act directly by interaction with specific somatostatin receptors known to be present on membranes of a variety of tumors, or indirectly by inhibiting release of growth factors known to stimulate neoplastic growth. Whatever the mechanism, somatostatin therapy may offer an additional period of symptom-free living in selected patients with solid neoplasms and in those patients with hypersecretory disorders from endocrine tumors. Somatostatin may prove to be a salient addition to cancer chemotherapy.

## References

1. Brazeau P, Vale W, Burgus R, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 1973; 179:77–79.
2. Krulich L, Dhariwal APS, McCann SM. Stimulatory and inhibitory effects of purified hypothalamic extracts on growth hormone release from rat pituitary *in vitro*. Endocrinology 1968; 83:783–790.
3. Lucey MR. Endogenous somatostatin and the gut. Gut 1986; 27: 457–467.
4. Newman JB, Lluis F, Townsend CM Jr. Somatostatin. *In* Thompson JC, Greeley GH Jr, Rayford PL, Townsend CM Jr, eds. Gastrointestinal Endocrinology. New York: McGraw-Hill Book Co, 1987, pp 286–299.
5. Reichlin S. Secretion of somatostatin and its physiologic function. J Lab Clin Med 1987; 109:320–326.
6. Longnecker SM. Somatostatin and octreotide: literature review and description of therapeutic activity in pancreatic neoplasia. Drug Intell Clin Pharm 1988; 22:99–106.
7. Reichlin S. Somatostatin (first of two parts). N Engl J Med 1983; 309:1495–1501.
8. Reichlin S. Somatostatin (second of two parts). N Engl J Med 1983; 309:1556–1563.
9. Price BA, Jaffe BM, Zinner MJ. Effect of exogenous somatostatin infusion on gastrointestinal blood flow and hormones in the conscious dog. Gastroenterology 1985; 88:80–85.
10. Tyden G, Samnegard H, Thulin L, et al. Circulatory effects of somatostatin in anesthetized man. Acta Chir Scand 1979; 145:443–446.
11. Lamberts SWJ, Uitterlinden P, del Pozo E. SMS 201-995 induces a continuous decline in circulating growth hormone and somatomedin-C levels during therapy of acromegalic patients for over two years. J Clin Endocrinol Metab 1987; 65:703–710.
12. Williams G, Burrin JM, Ball JA, et al. Effective and lasting growth-hormone suppression in active acromegaly with oral administration of somatostatin analogue SMS 201–995. Lancet 1986; 2: 774–777.
13. Ellison EC, Garner WL, Mekhjian HS, et al. Successful treatment of pancreatic ascites with somatostatin analog (SMS 201–995). Gastroenterology 1986; 90:1405(Abst).
14. Santangelo WC, O'Dorisio TM, Kim JG, et al. Pancreatic cholera syndrome: effect of a synthetic somatostatin analog on intestinal water and ion transport. Ann Intern Med 1985; 103:363–367.
15. Ellison EC, O'Dorisio TM, Elkammas E, et al. Long-acting somatostatin analog inhibits calcium and secretin stimulated gastrin release in the Zollinger-Ellison syndrome. Gastroenterology 1986; 90:1405(Abst).
16. Ellison EC, O'Dorisio TM, Sparks J, et al. Observations on the effect of a somatostatin analog in the Zollinger-Ellison syndronme: implications for the treatment of apudomas. Surgery 1986; 100: 437–444.
17. Souquet J-C, Sassolas G, Forichon J, et al. Clinical and hormonal effects of a long-acting somatostatin analogue in pancreatic endocrine tumors and in carcinoid syndrome. Cancer 1987; 59: 1654–1660.
18. Vinik AI, Tsai S, Moattari AR, Cheung P. Somatostatin analogue (SMS 201–995) in patients with gastrinomas. Surgery 1988; 104: 834–842.
19. Osei K, O'Dorisio TM. Malignant insulinoma: effects of a somatostatin analog (compound 201–995) on serum glucose, growth, and gastro-entero-pancreatic hormones. Ann Int Med 1985; 103: 223–225.
20. Reubi JC. A somatostatin analogue inhibits chondrosarcoma and insulinoma tumour growth. Acta Endocrinologica 1985; 109:108–114.
21. O'Dorisio TM, Gaginella TS, Mekhjian HS, et al. Somatostatin and analogues in the treatment of VIPoma. Ann NY Acad Sci 1988; 527:528–535.
22. Juby LD, Burke DA, Axon ATR. Somatostatin analogue SMS 201–995 long term therapy for vipoma. Postgraduate Med J 1987; 63:287–289.
23. Kraenzlin ME, Ch'ng JLC, Wood SM, et al. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. Gastroenterology 1985; 88:185–187.
24. Clements D, Elias E. Regression of metastatic VIPoma with somatostatin analogue SMS 201–995. Lancet 1985; 1:874–875.
25. Boden G, Ryan IG, Eisenschmid BL, et al. Treatment of inoperable glucagonoma with the long-acting somatostatin analogue SMS 201–995. N Engl J Med 1986; 314:1686–1689.
26. Altimari AF, Bhoopalam N, O'Dorsio T, et al. Use of a somatostatin analog (SMS 201–995) in the glucagonoma syndrome. Surgery 1986; 100:989–995.
27. Ahlman H, Ahlund L, Dahlstrom A, et al. Use of a somatostatin analogue in association with surgery and hepatic arterial embolisation in the treatment of the carcinoid syndrome. Br J Cancer 1987; 56:840–842.

28. Kvols LK, Moertel CG, O'Connell MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986; 315:663–666.
29. Schally AV. Oncological applications of somatostatin analogues. Cancer Res 1988; 48:6977–6985.
30. Rose DP, Gottardis M, Noonan JJ. Rat mammary carcinoma regressions during suppression of serum growth hormone and prolactin. Anticancer Res 1983; 3:323–326.
31. Setyono-Han B, Henkelman MS, Foekens JA, Klijn JGM. Direct inhibitory effects of somatostatin (analogues) on the growth of human breast cancer cells. Cancer Res 1987; 47:1566–1570.
32. Weber C, Merriam L, Koschitzky T, et al. Inhibition of growth of human breast carcinomas in vivo by somatostatin analogue, SMS 201–995, treatment of nude mouse xenografts. Surgery 1989; 106:416–422.
33. Scambia G, Panici PB, Baiocchi G, et al. Antiproliferative effects of somatostatin and the somatostatin analog SMS 201–995 on three human breast cancer cell lines. J Cancer Res Clin Oncol 1988; 114:306–308.
34. Schally AV, Comaru-Schally AM, Redding TW. Antitumor effects of analogs of hypothalamic hormones in endocrine-dependent cancers. Proc Soc Exp Biol Med 1984; 175:259–281.
35. Schally AV, Redding TW. Somatostatin analogs as adjuncts to agonists of luteinizing hormone-releasing hormone in the treatment of experimental prostate cancer. Proc Natl Acad Sci USA 1987; 84:7275–7279.
36. Zalatnai A, Paz-Bouza JI, Redding TW, Schally AV. Histologic changes in the rat prostate cancer model after treatment with somatostatin analogs and D-Trp-6-LH-RH. The Prostate 1988; 12:85–98.
37. Murphy WA, Lance VA, Moreau S, et al. Inhibition of rat prostate tumor growth by an octapeptide analog of somatostatin. Life Sci 1987; 40:2515–2522.
38. Smith JP, Solomon TE. Effects of gastrin, proglumide, and somatostatin on growth of human colon cancer. Gastroenterology 1988; 95:1541–1548.
39. Singh P, Le S, Townsend CM Jr, et al. A long acting somatostatin analog (SRIF) (201–995) and proglumide (PGL) inhibit the trophic and gastrin receptor (GR) regulatory effects of pentagastrin (PG) on mouse colon cancer (MC-26) cells in vivo. Gastroenterology 1986; 90:1636(Abst).
40. Milhoan RA, Milhoan LH, Trudel JL, et al. Somatostatin and $\alpha$-difluoromethylornithine (DFMO) have additive inhibitory effects on growth of human colon carcinoma (HCC) in vivo. Biomed Res 1988; 9:30(Abst).
41. Redding TW, Schally AV. Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones. Proc Natl Acad Sci USA 1984; 81:248–252.
42. Upp JR Jr, Olson D, Poston GJ, et al.Inhibition of growth of two human pancreatic adenocarcinomas in vivo by somatostatin analog SMS 201–995. Am J Surg 1988; 155:29–35.
43. Hierowski MT, Liebow C, du Sapin K, Schally AV. Stimulation by somatostatin of dephosphorylation of membrane proteins in pancreatic cancer MIA PaCa-2 cell line. FEBS Lett 1985; 179: 252–256.
44. Milhoan RA, Trudel JL, Lawrence JP, et al. Somatostatin inhibits growth of human small cell lung carcinoma in vivo. Surg Forum 1988; 39:438–439.
45. Taylor JE, Bogden AE, Moreau J-P, Coy DH. In vitro and in vivo inhibition of human small cell lung carcinoma (NCI-H69) growth by a somatostatin analogue. Biochem Biophys Res Commun 1988; 153:81–86.
46. Mascardo RN, Sherline P. Somatostatin inhibits rapid centrosomal separation and cell proliferation induced by epidermal growth factor. Endocrinology 1982; 111:1394–1396.
47. Davies RR, Miller M, Turner SJ, et al. Effects of somatostatin analogue SMS 201–995 in normal man. Clin Endocrinol 1986; 24: 665–674.
48. Bauer W, Briner U, Doepfner W, et al. SMS 201–995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31:1133–1140.
49. Williams G, Anderson JV, Williams SJ, Bloom SR. Clinical evaluation of SMS 201–995. Long-term treatment in gut neuroendocrine tumours, efficacy of oral administration, and possible use in non-tumoural inappropriate TSH hypersecretion. Acta Endocrinologica 1987; suppl 286:26–36.
50. Cai R-Z, Szoke B, Lu R, et al. Synthesis and biological activity of highly potent octapeptide analogs of somatostatin. Proc Natl Acad Sci USA 1986; 83:1896–1900.
51. Lamberts SWJ, Koper JW, Reubi J-C. Potential role of somatostatin analogues in the treatment of cancer. Eur J Clin Invest 1987; 17: 281–287.
52. Werner H, Amarant T, Millar RP, Fridkin M, Koch Y. Immunoreactive and biologically active somatostatin in human and sheep milk. Eur J Biochem 1985; 148:353–357.
53. Reubi JC, Maurer R, von Werder K, et al. Somatostatin receptors in human endocrine tumors. Cancer Res 1987; 47:551–558.
54. Spring-Mills EJ, Stearns SB, Numann PJ, Smith PH. Immunocytochemical localization of insulin- and somatostatin-like material in human breast tumors. Life Sci 1984; 35:185–190.
55. Klijn JGM, Setyono-Han B, Bakker GH, Foekens JA. Effects of somatostatin analog (SMS-A) treatment (sandostatin) in experimental and human cancer. Eur J Cancer Clin Oncol 1986; 22: 727.
56. Lippman ME, Dickson RB, Kasid A, et al. Autocrine and paracrine growth regulation of human breast cancer. J Steroid Biochem 1986; 24:147–154.
57. Erisman MD, Linnoila RI, Hernandez O, et al. Human lung small-cell carcinoma contains bombesin. Proc Natl Acad Sci USA 1982; 79:2379–2383.
58. Abe K, Kameya T, Yamaguchi K, et al. Hormone-producing lung cancers. Endocrinologic and morphologic studies. *In* Becker KL, Gazdar AF, eds. The Endocrine Lung in Health & Disease. Philadelphia: WB Saunders, 1984, pp 549–595.
59. Gazdar AF. The biology of endocrine tumors of the lung. An overview. *In* Becker KL, Gazdar AF, eds. The Endocrine Lung in Health & Disease. Philadelphia: WB Saunders, 1984, pp 448–459.
60. Catane R, Lichter A, Lee YJ, Brereton HD, Schwade JG, Glatstein E. Small cell lung cancer: analysis of treatment factors contributing to prolonged survival. Cancer 1981; 48:1936–1943.
61. Cuttita F, Carney DN, Mulshine J, et al. Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. Nature 1985; 316:823–826.
62. Moody TW, Bertness V, Carney DN. Bombesin-like peptides and receptors in human tumor cell lines. Peptides 1983; 4:683–686.
63. Yoshizaki K, de Bock V, Takai I, et al. Bombesin-like peptides in human small cell carcinoma of the lung. Regul Pept 1986; 14: 11–20.
64. Sorenson GD, Bloom SR, Ghatei MA, et al. Bombesin production by human small cell carcinoma of the lung. Regul Pept 1982; 4: 59–66.
65. Walsh JH, Reeve JR Jr. Mammalian bombesin-like peptides: neuromodulators of gastric function and autocrine regulators of lung cancer growth. Peptides 1985; 6:63–68.
66. Wood SM, Wood JR, Ghatei MA, et al. Bombesin, somatostatin and neurotensin-like immunoreactivity in bronchial carcinoma. J Clin Endocrinol Metab 1981; 53:1310–1312.
67. Alexander RW, Upp JR Jr, Poston GJ, et al. Effects of bombesin on growth of human small cell lung carcinoma in vivo. Cancer Res 1988; 48:1439–1441.
68. Upp JR Jr, Singh P, Townsend CM Jr, Thompson JC. The clinical significance of gastrin receptors in human colon cancers. Cancer Res 1989; 49:488–492.
69. Winsett OE, Townsend CM Jr, Glass EJ, Thompson JC. Gastrin stimulates growth of colon cancer. Surgery 1986; 99:302–307.
70. Upp JR Jr, Singh P, Townsend CM Jr, Thompson JC. Predicting response to endocrine therapy in human pancreatic cancer with cholecystokinin receptors. Gastroenterology 1987; 92:1677(Abst).
71. Townsend CM Jr, Franklin RB, Watson LC, et al. Stimulation of pancreatic cancer growth by caerulein and secretin. Surg Forum 1981; 32:228–229.

72. Liebow C, Hierowski M, duSapin K. Hormonal control of pancreatic cancer growth. Pancreas 1986; 1:44–48.
73. Krejs GJ. Proceedings of a Symposium. Gastrointestinal endocrine tumors: diagnosis and management. Role of somatostatin analogue SMS 201–995. Am J Med 1987; 82(Suppl 5B):1–99.
74. Bloom SR, Greenwood C. Proceedings of somatostatin '85. Chemical, physiological, and clinical advances. Scand J Gastroenterol 1986; 21(Suppl 119):1–274.
75. Maton PN, Gardner JD, Jensen RT. Use of long-acting somatostatin analog SMS 201–995 in patients with pancreatic islet cell tumors. Dig Dis Sci 1989; 34:28S–39S.
76. Gorden P, Comi RJ, Maton PN, Go VLW. Somatostatin and somatostatin analogue (SMS 201–995) in treatment of hormone-secreting tumors of the pituitary and gastrointestinal tract and non-neoplastic diseases of the gut. Ann Internal Med. 1989; 110: 35–50.
77. Lamberts SWJ, Reubi J-C, Uiterlinden P, et al. Studies on the mechanism of action of the inhibitory effect of the somatostatin analog SMS 201–995 on the growth of the prolactin/adrenocorticotropin-secreting pituitary tumor 7315a. Endocrinology 1986; 118:2188–2194.
78. Allen E, Evers BM, Townsend CM Jr, et al. Somatostatin analog (201–995) and $\alpha$-difluoromethylornithine (DFMO) inhibit growth of human carcinoid tumor. Surg Forum 1989; 40:22–24.
79. Upp JR Jr, Alexander RW, Poston GJ, et al. Inhibition of a human malignant carcinoid growing in nude mice. Gastroenterology 1987; 92:1643(Abst).
80. Shepherd JJ, Senator GB. Regression of liver metastases in patient with gastric-secreting tumour treated with SMS 201–995. Lancet 1986; ii:574.
81. Wiedenmann B, Rath U, Radsch R, Becker F, Kommerell B. Tumor regression of an ileal carcinoid under the treatment with the somatostatin analogue SMS 201–995. Klin Wochenschr 1988; 66: 75–77.

# The Spectrum of Portal Vein Thrombosis in Liver Transplantation

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**Thrombosis of the portal vein with or without patency of its tributaries used to be a contraindication to orthotopic liver transplantation (OLTX) until quite recently. Rapid progress in the surgical technique of OLTX in the last few years has demonstrated that most patients with portal vein thrombosis can be safely and successfully transplanted. Presented here is a series of 34 patients with portal vein thrombosis transplanted at the University of Pittsburgh since 1984. The various techniques used to treat various forms of thrombosis are described. The survival rate for this series was 67.6% (23 of 34 patients). Survival was best for patients who underwent phlebothrombectomy or placement of a jump graft from the superior mesenteric vein. The survival rate also correlated with the amount of blood required for transfusion during surgery. Overall it is concluded that a vast majority of the patients with thrombosis of the portal system can be technically transplanted and that their survival rate is comparable to that of patients with patent portal vein.**

THROMBOSIS OF THE portal vein (PV) and/or its tributaries (portal system) has been a formidable challenge in orthotopic liver transplantation (OLTX). Although this complication of end-stage liver disease was once a relative contraindication to OLTX if known in advance,[1-3] the need to treat unexpected thromboses uncovered during operation soon led to the development of venous grafting procedures.[4,5] During the last few years, we used increasingly sophisticated techniques to treat splanchnic venous thrombosis, thereby widening the indications for OLTX. Presently almost all patients with portal system thrombosis, even of very extensive nature, can have orthotopic transplantation.

## Methods

### *Surgical Techniques*

If portal system thrombosis is suspected before operation or discovered at the time of transplantation, venogram can be obtained by cannulating one of the branches of the ileocolic vein or the inferior mesenteric vein (Fig. 1). Accurate knowledge of the patient's anatomy is essential to plan subsequent steps. One of the deviations from normal practice is the use of a single venovenous bypass (femoral to axillary vein), omitting the usual decompression of the splanchnic system during the anhepatic phase.[6,7]

The extent of the thrombosis may vary from segmental of the PV only (Fig. 2A) to extremely extensive, with involvement of all the major splanchnic veins (Fig. 2D). If the segmental thrombosis is high enough that the portal vein can be encircled and clamped superior to the pancreas (Fig. 3), the usual venous anastomosis can be performed (Fig. 4A) or a short interposition vein graft from the donor liver can be inserted (Fig. 4B). Efforts at this encirclement can be hazardous, especially if this is near the retropancreatic confluence of the superior mesenteric vein (SMV) and splenic vein (SV). Hemorrhage during such a dissection forced us, in two cases, to transect the pancreas and ultimately to replace the PV and SMV with donor vein grafts (Fig. 5). Iliac veins are harvested routinely from the liver donors and they can prove life saving under these circumstances.

An alternative technique, and one that is more applicable to extensive thromboses, is a jump graft from the

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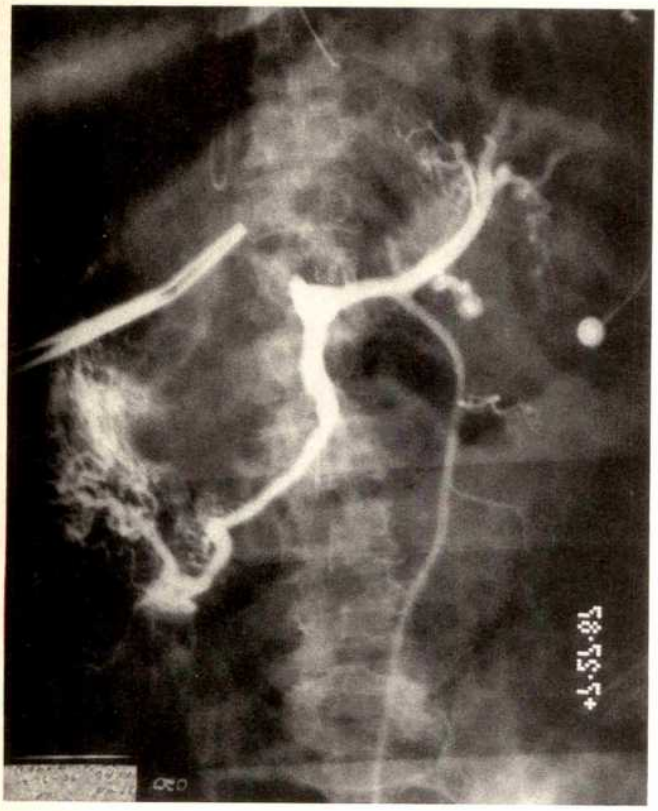


FIG. 1. Portal system angiogram performed through a catheter inserted in the inferior mesenteric vein, showing complete thrombosis of the portal vein.

superior mesenteric vein or one of its tributaries.[8,9] This is our preferred approach for the complex thromboses shown in Figure 2B to D. The method can be used even if there has been previous thrombosis of the SMV, providing there is recanalization and enough normal wall to allow an anastomosis. A free segment of donor iliac vein, including the common and external portions, is anastomosed end-to-side to the SMV, then tunneled through the avascular window anterior to the pancreas, beneath the pylorus and into the hepatic hilum. The tunnel can be either to the right or left of the middle colic vein, depending on the straightest route. This graft can then be anastomosed easily to the donor's portal vein (Fig. 6). In some of our early cases, this graft was brought through the natural infrapancreatic tunnel after teasing out the thrombosed SMV, but hemorrhage from the bed (Fig. 5) was too uncontrolled for this to be practical.

Even if there has been previous thrombosis of the PV and recanalization with thickening of the walls (Fig. 7), such a vessel can be satisfactory for venous anastomosis, providing the flow is good. However very careful suturing is required because the abnormal wall of the recipient PV can be not only friable but also subject to layer separation. Perfect apposition of the endothelium of the two vessels is mandatory in what may be considered to be a circumferential intimorrhaphy (Figure 8A and B). Flushing of the recanalized PV with heparinized saline solution and

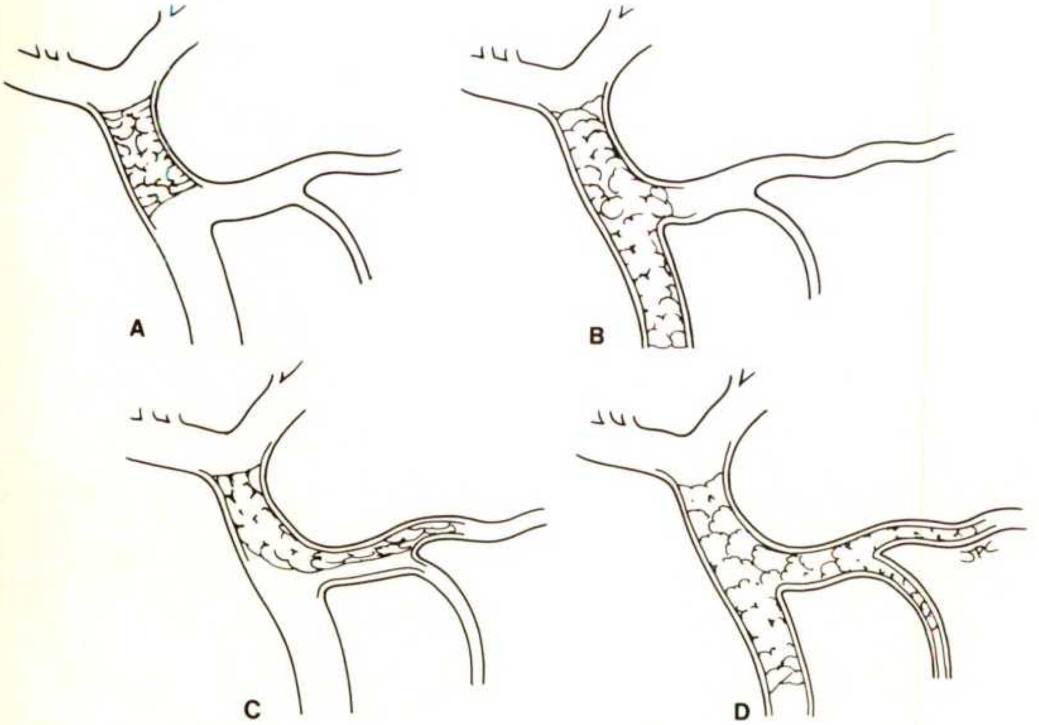


FIG. 2. The different types of thrombosis of the portal vein and its tributaries are shown.

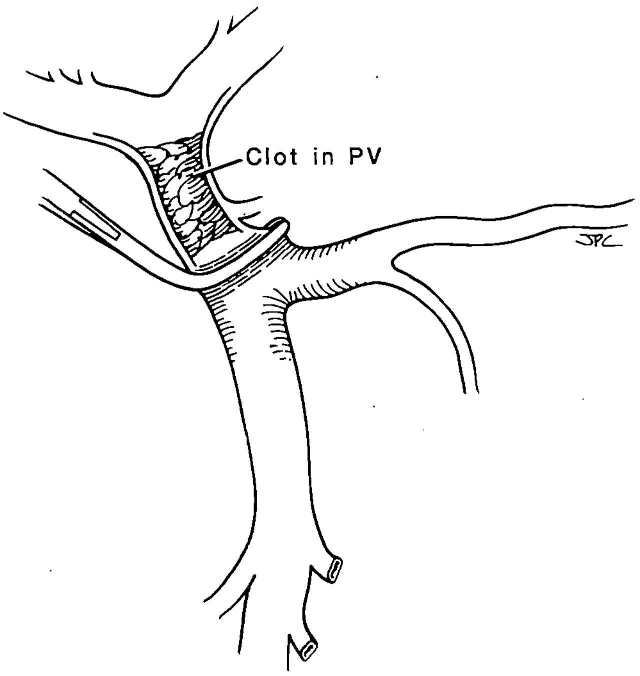


FIG. 3. Position of the portal clamp at the confluence of the superior mesenteric (SMV) and splenic (SV) veins in thrombosis of the portal vein only.

probing with Fogarty or Foley catheters may be indicated before anastomosis and/or before restoring flow to the liver.

If all the major splanchnic vessels (PV, SMV, and SV) are thrombosed (Fig. 2D), the situation may still be rectifiable. If a very large coronary vein is present, the donor's PV can be anastomosed in an end-to-side fashion to this vessel (Fig. 9). This procedure was first performed on a patient 6 years ago who is still well. Alternatively a venous collateral can be anastomosed by a bridge vein graft to the liver portal vein (Fig. 10) if the flow is inadequate after phlebothrombectomy and other efforts.

In one patient whose portal flow was still considered subobtimal, the graft portal was arterialized from the donor's splenic artery stump (Fig. 11). This is a well-known experimental procedure[10] that has been used clinically to arterialize the central portal vein after completely diverting portocaval shunt.[11,12] The outcome in our patient was excellent, with the patient becoming perfectly well 10 months later.

When not even a large coronary vein is present, division of the portal vein high in the liver hilum and extensive embolectomy can usually establish sufficient portal flow for revascularization of the donor liver. The embolectomy is performed with a combination of scissor dissection, use of ring clamps, and Fogarty and/or Foley catheters (Figs. 12 to 14). The portal system is then flushed extensively with heparinized saline to remove lose thrombus and prevent rethrombosis during cross-clamping.

*Patient Material*

At the University of Pittsburgh 1585 patients were transplanted between April 1, 1986 and October 31, 1989. Of these, 34 patients (2.1%) had thrombosis of the portal vein. Fourteen patients (41.2%) had postnecrotic cirrhosis, 8 patients (23.5%) had Laennec's cirrhosis, 3 patients (8.8%) had cryptogenic or autoimmune hepatitis, and 2

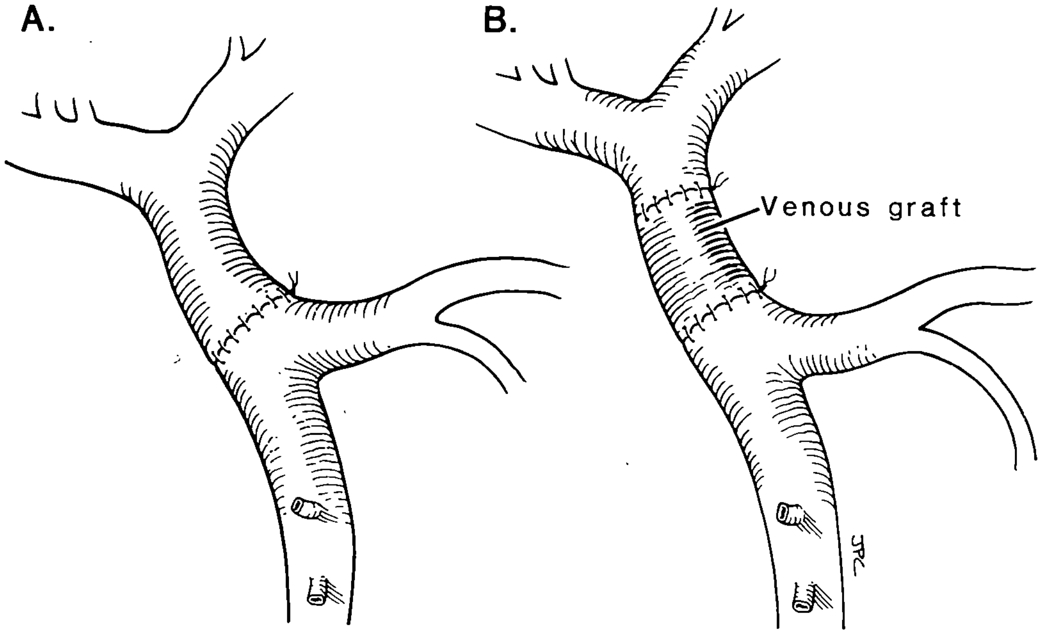


FIG. 4. (A) Direct anastomosis of the donor portal vein to the recipient confluence of the SMV and SV (B) Short free vein interposition graft used between the donor and recipient's portal veins.

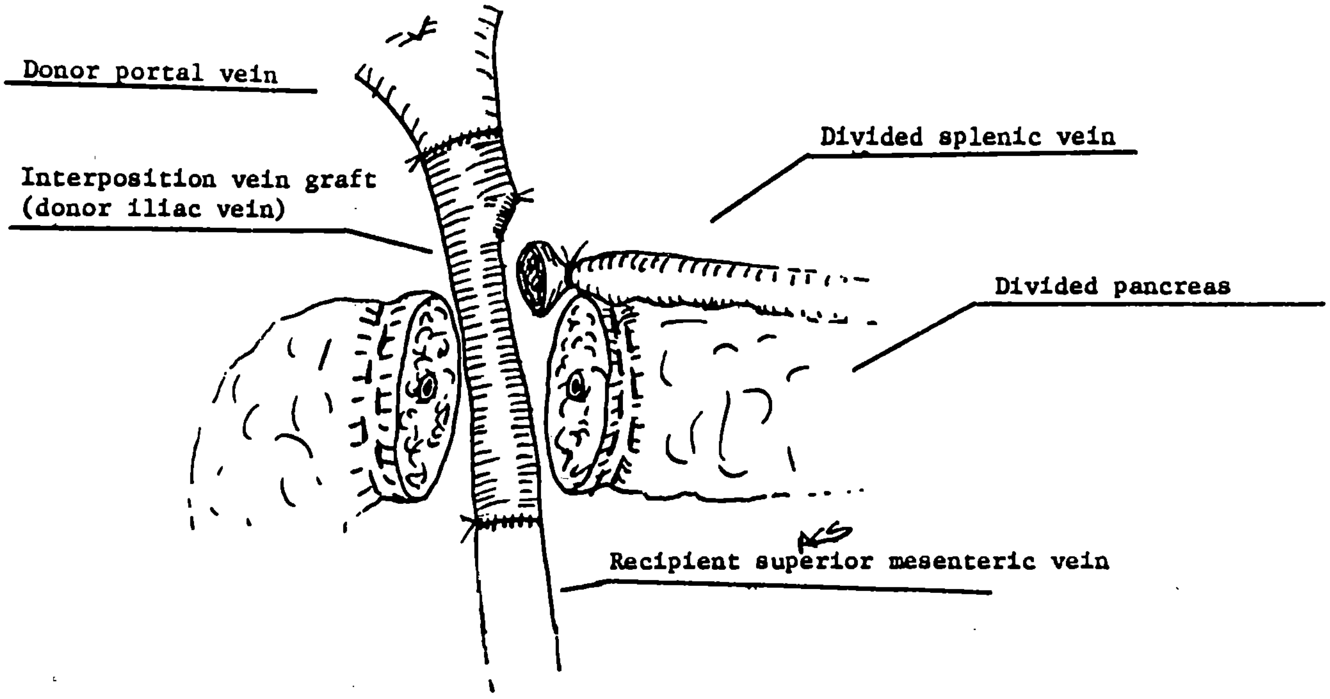


FIG. 5. Division of the pancreas for access to the retropancreatic superior mesenteric vein, with placement of a free interposition vein graft.

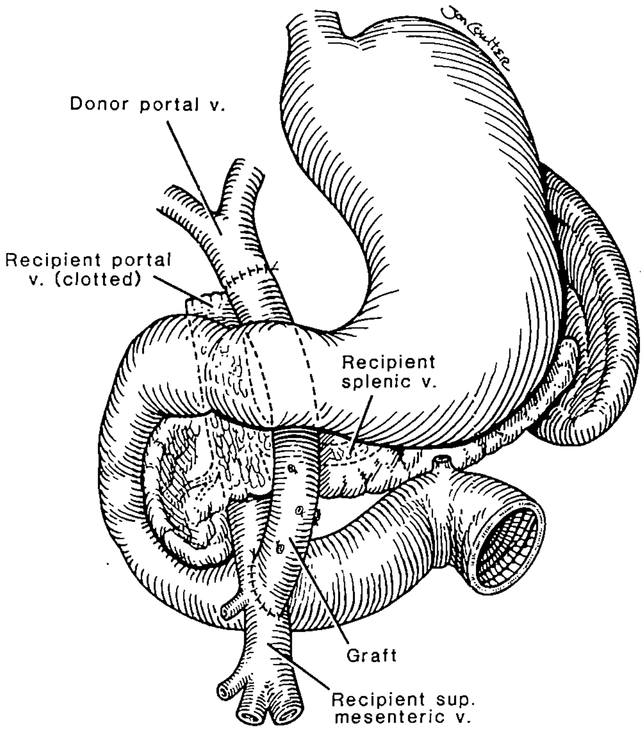


FIG. 6. Venous jump graft, from the infrapancreatic superior mesenteric vein into the donor portal vein, tunnelled in between the pancreas and the pylorus.

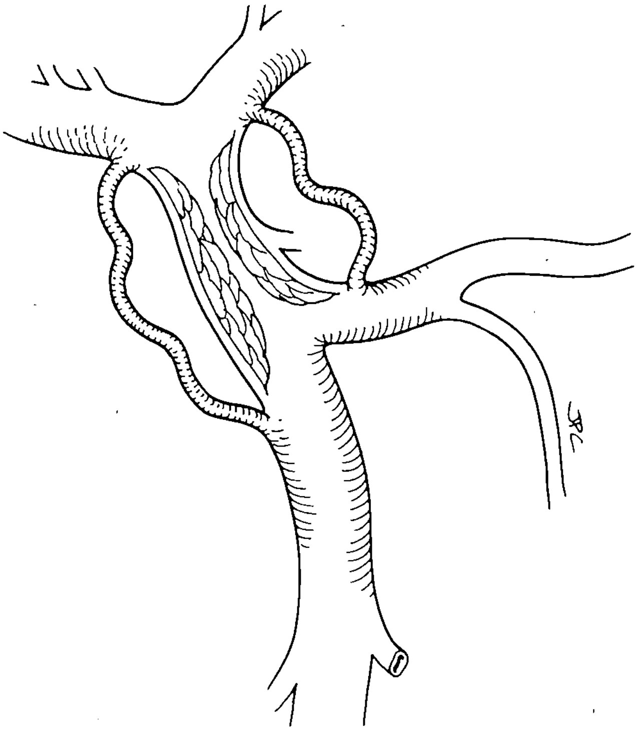
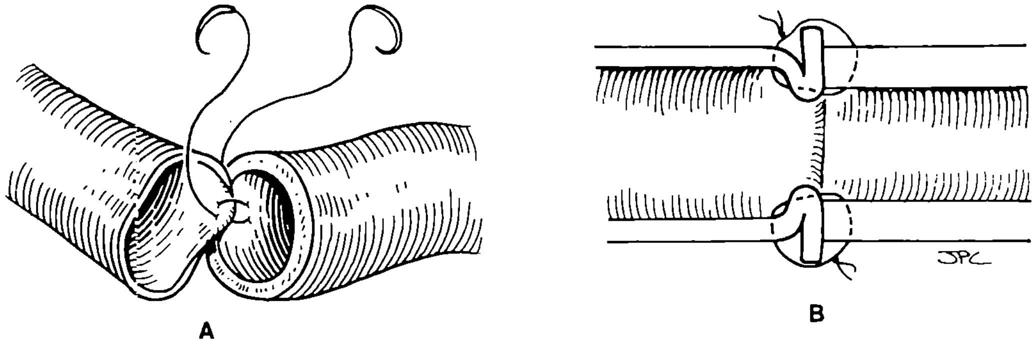


FIG. 7. Cavernomatous transformation of a thrombosed portal vein.



FIGS. 8A and B. Both A and B show details of the anastomosis of a normal, thin-walled donor portal vein to a thick-walled recipient portal vein.

patients (5.9%) had congenital biliary atresia and primary sclerosing cholangitis. Congenital hepatitis, primary biliary cirrhosis, secondary biliary cirrhosis, hemochromatosis with associated hepatoma, and Wilson's disease with a previous distal splenorenal shunt were found in five patients (2.9%) (one condition in each patient). The preoperative sonographic examination of the liver with Doppler probe accurately diagnosed the portal vein thrombosis in only 16 (47.1%) patients. In 15 other patients of the entire transplant population (1%), a false-positive report of portal vein thrombosis was not verified at the time of transplantation.

### Results

Twenty three (67.6%) of the patients had thrombosis of the portal vein only with sparing of the confluence of the SV and SMV (group 1). Seventeen (73.9%) of these patients survived. In contrast, the survival rate was only 6 (54.5%) of the 11 patients who had extensive thromboses of the distal splanchnic systems (group 2; Fig. 15). One of the deaths in group 1 was from recurrent hepatoma 6 months later. The recurrence had invaded and reoccluded the portal vein.

Two of the eleven deaths in the whole group occurred during the operation. Mortality was correlated with blood loss, which ranged from 4 to 160 units (mean 35.6 ± 40.6 SD). Seventeen of twenty patients (85%) survived the operation when less then 30 units of blood were given compared to 7 of 14 patients (50%) with transfusions greater than this ($p < 0.005$; Fig. 15).

The venous jump grafts were successful in 11 of 14 cases (78.6%) compared to only 8 of 13 cases (61.5%) when direct thrombectomy or interposition grafts were used (Fig. 15). In five patients with extensive thrombosis

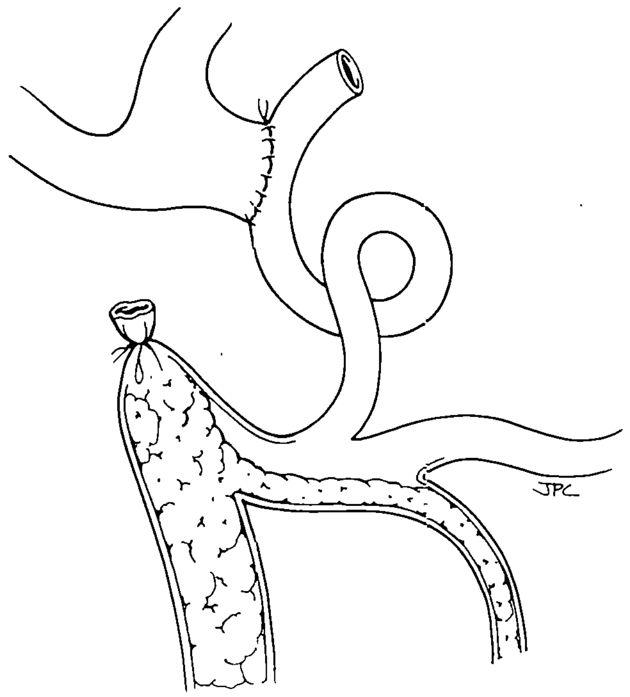


FIG. 9. Anastomosis of the donor portal vein to a large patent recipient coronary vein in the case of an extensive thrombosis of the portal system.

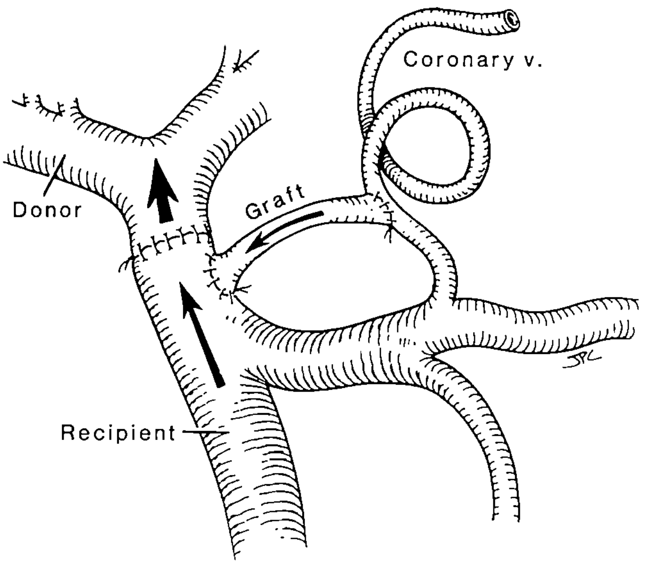


FIG. 10. Interposition vein graft between the recipient coronary vein and either the recipient's or the donor's portal vein, intended to increase the flow through the portal system.

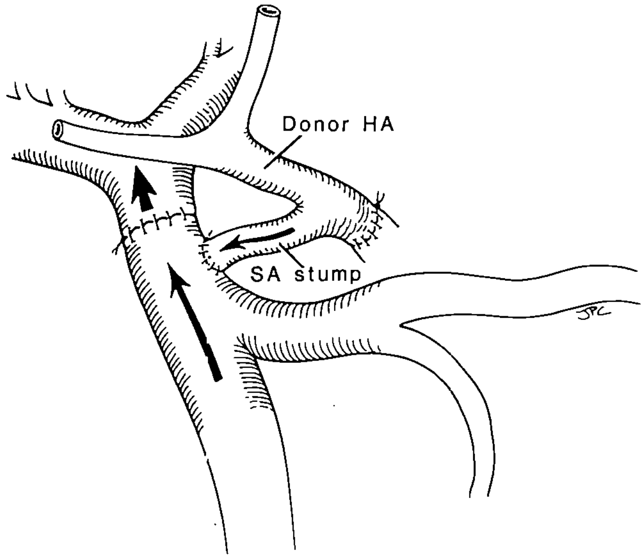


FIG. 11. Arterilization of the portal vein using the stump of the donor splenic artery.

of the mesenteric system in which declotting of the portal vein and its tributaries as well as anticoagulation were used, the survival rate was 100%. Although encouraging, the number of these high-risk patients is too small to allow conclusions about this form of treatment. The remaining two patients were excluded because they died during operation.

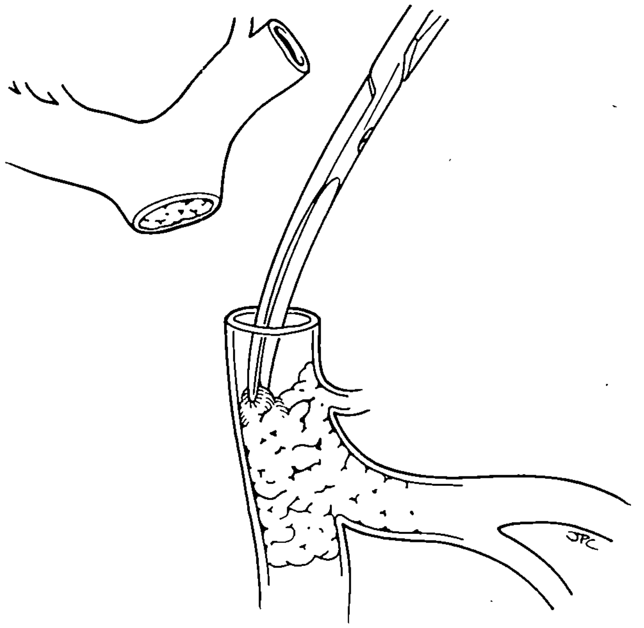


FIG. 12. In extensive thrombosis of the portal system, phlebothrombectomy can be accomplished, first by using sharp dissection with scissors.

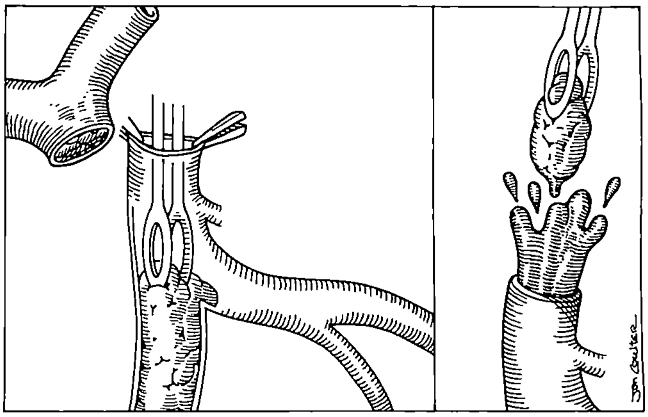


FIG. 13. The phlebothrombectomy is continued with the use of a ring clamp that can grab either hard or soft thrombus and safely remove it.

## Discussion

This experience illustrates how a major technical hurdle in OLTX was overcome using increasingly simple solutions to the problems that actually have become more complex. This tendency toward streamlining is evident in all of the technical aspects of liver transplantation.

Most PV thromboses occurred in patients with postnecrotic cirrhosis. Unexpected thromboses were found most commonly in patients with severely shrunken livers and in those with sudden deterioration after a period of seeming clinical stability. Negative ultrasound reports frequently were erroneous. Patients with Laennec's cirrhosis are also at high risk for PV thrombosis. Before the availability of transplantation, the incidence of this complication was said to be about 11%[13]; however more recent studies suggest that the incidence is only 0.5%.[14] Portal vein thrombosis may be more common in male patients.

In our series, the extent of the thrombosis appeared to influence the outcome, as did the amount of blood needed at operation. That these two variable are parallel is not surprising because the technical difficulties posed by extensive venous disease can come close to the ultimate challenge. However some of the most serious hemorrhages occurred in patients whose thromboses did not extend into the SV or SMV. In earlier days, great efforts were made to dissect back to the open confluence of these vessels for placement of interposition grafts. This necessitated invasion of the superior pancreatic area, which, under these circumstances, is especially rich in collaterals. Today we abandon these efforts early if they prove to be difficult in favor of an extra-anatomic jump graft from the SMV. The consequences since 1987 have been better patient and graft survival and a reduced incidence of post-transplant pancreatitis. Our recent experience with five patients who were beyond help even with jump graft techniques has been encouraging. These patients who underwent

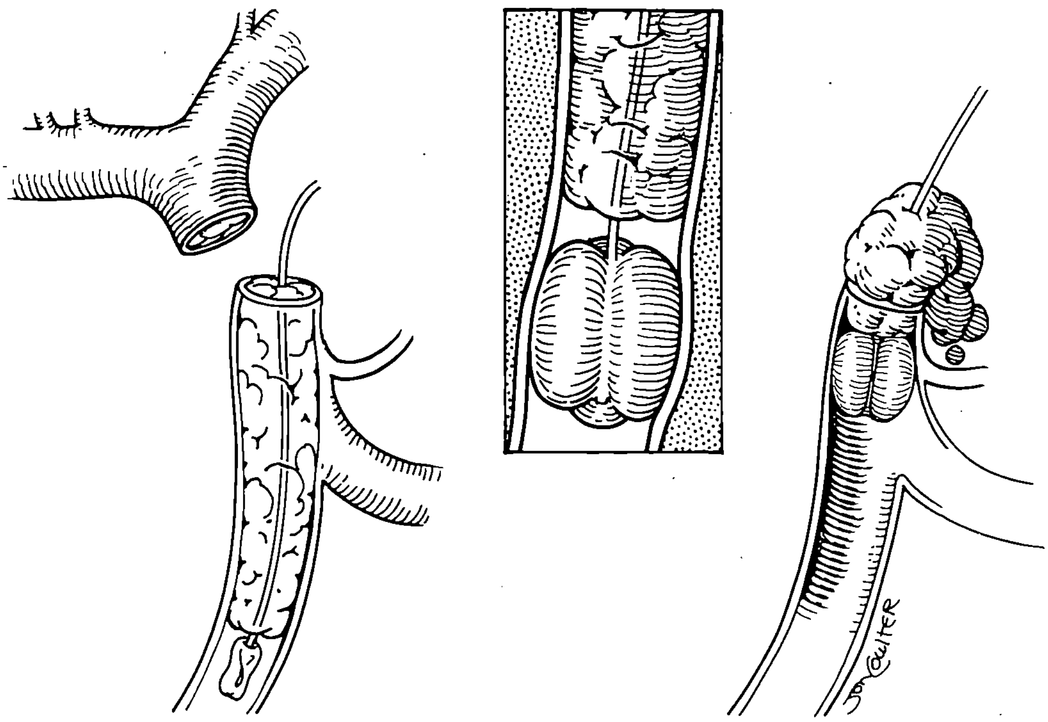


FIG. 14. Another alternative for the phlebothrombectomy is the use of Fogarty balloon catheters or Foley catheters.

thrombectomies and make-shift procedures (including central portal arterialization) and later anticoagulation may be better candidates than we previously realized.

An algorhithm has been developed for approaching portal vein thrombosis (Fig. 16). This algorhithm permits a flexible approach to the operation that can be modified on the basis of the sometimes unexpected findings that are encountered. It is possible that almost all patients with portal system thrombosis can undergo successful liver replacement.

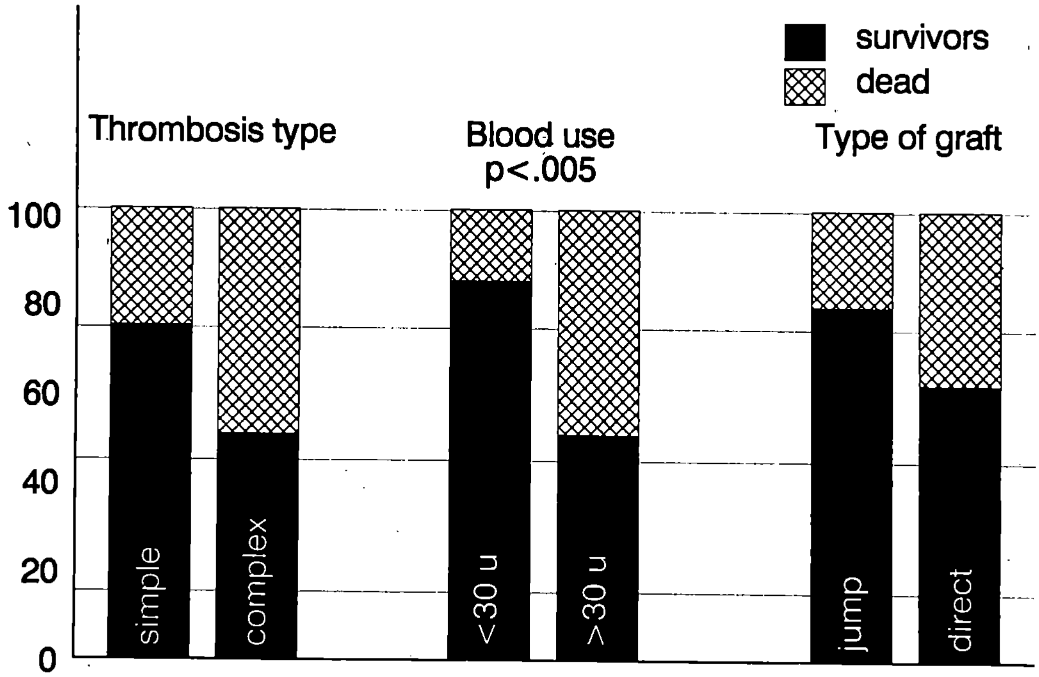


FIG. 15. Difference in survival depending on thrombosis type, blood loss, and type of graft.

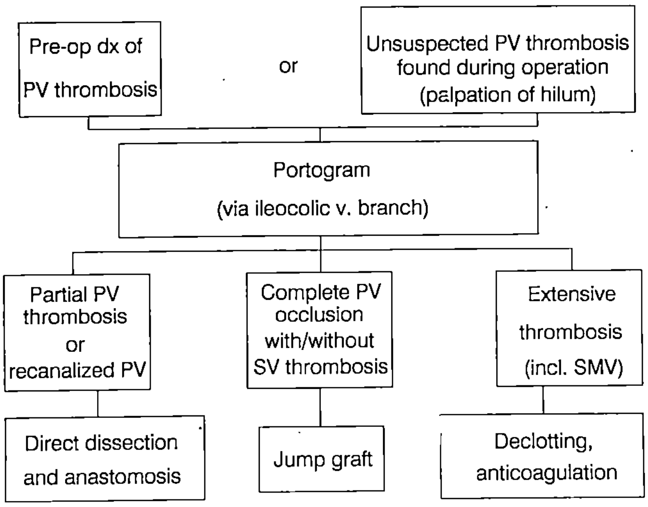

Pre-op dx of PV thrombosis
or
Unsuspected PV thrombosis found during operation (palpation of hilum)
Portogram (via ileocolic v. branch)
Partial PV thrombosis or recanalized PV
Complete PV occlusion with/without SV thrombosis
Extensive thrombosis (incl. SMV)
Direct dissection and anastomosis
Jump graft
Declotting, anticoagulation

FIG. 16. Algorithm for approaching patients with PV thrombosis.

## Acknowledgment

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## References

1. Cardella JF, Castaneda-Zuniga WR, Hunter D, et al. Angiographic and interventional radiologic considerations in liver transplantation. Am J Roengenol 1986; 146(1):143-153.
2. Zajko AB, Bron KM, Starzl TE, et al. Angiography of liver transplantation patients. Radiology 1985; 157(2):305-311.
3. VanThiel DH, Schade RR, Starzl TE, et al. Liver transplantation in adults. Hepatology 1982; 2:637-640.
4. Starzl TE, Halgrimson CG, Koep LJ, et al. Vascular homografts from cadaveric organ donors. Surg Gynecol Obstet 1979; 149: 76-77.
5. Shaw WB Jr, Iwatsuki S, Bron KM, et al. Portal vein grafts in hepatic transplantation. Surg Gynecol Obstet 1985; 161:66-68.
6. Griffith BP, Shaw WB JR, Hardesty RL, et al. Veno-venous bypass without systemic anticoagulation in canine and human liver transplantation. Surg Forum 1983; 34:380-382.
7. Shaw BW jr, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 1984; 200:524-534.
8. Tzakis AG, Todo S, Starzl TE. The anterior route for arterial graft conduits in liver transplantation. Transplant Int 1989; 2:121.
9. Sheil AGR, Thompson JF, Stephen MS, et al. Meso-portal graft for thrombosed portal vein in liver transplantation. Clin Transpantation 1987; 1:18-20.
10. Asakawa H, Kasai S, Mito M. Flow- and pressure-adapted portal arterialization in dogs. Jpn J Surg 1985; 15(4):291-298.
11. Otte JB, Reynaert M, De Hemptinne B, et al. Arterialization of the portal vein in conjunction with a therapeutic portocaval shunt. Hemodynamic investigations and results in 75 patients. Ann Surg 1982; 196:656-663.
12. Sheil AGR, Thompson JF, Stephen MS, et al. Donor portal vein arterialization during liver transplantation. Transpl Proc 1989; 21(1):2343-2344.
13. Hunt AH, Whittard BR. Thrombosis of the portal vein in cirrhosis hepatis. Lancet 1954; i:281-283.
14. Okuda K, Ohnishi K, Kimura K, et al. Incidence of portal vein thrombosis in liver cirrhosis. Gastroenterology 1985; 89:279-286.

**TORADOL® IM (ketorolac tromethamine)**

**Brief Summary**

TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24–48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. *Drug Interactions:* TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. *In vitro* binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5–10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), *in vitro* binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. *Carcinogenesis, Mutagenesis, and Impairment of Fertility:* Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. *Pregnancy:* Pregnancy Category B: Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. *Labor and Delivery:* TORADOL is not recommended for use during labor and delivery. *Lactation and Nursing:* After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. *Pediatric Use:* TORADOL is not recommended for use in children. *Use in the Elderly:* Because ketorolac is cleared more slowly by the elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. *Incidence greater than 1%:* Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%–9%. Reactions occurring in less than 3% are unmarked. *Incidence 1% or less:* Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥ 6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. *In vitro*, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses > 100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

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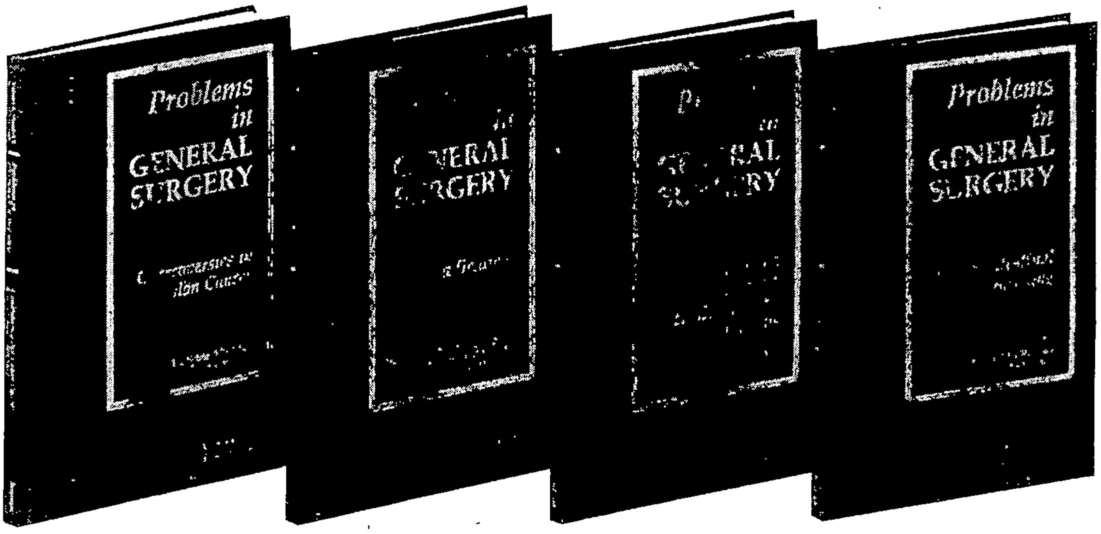

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# Severe Gastrointestinal Hemorrhage in Crohn's Disease

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**Twenty-one of fifteen hundred twenty-six patients with Crohn's disease (CD) treated at The Mount Sinai Hospital between 1960 and 1986 developed severe gastrointestinal hemorrhage. There were 26 separate episodes of severe hemorrhage: 17 patients bled only once, three bled twice, and one bled three times. The frequency of bleeding was significantly higher among patients with colonic involvement (17 of 929; 1.9%) than among those with small bowel disease alone (4 of 597; 0.7%) ($p < 0.001$). Twelve patients required surgery on 13 occasions, which involved colon resection in all but one case. Eleven of these patients underwent surgery during their first hemorrhagic episodes, and 1 of 11 had a second operation for recurrent bleeding; the 12th patient, whose first hemorrhage had been treated medically, had surgery during a repeated episode of hemorrhage. The precise bleeding points could be located in only 2 of the 26 bleeding episodes, both at the ileocecal area. Three patients died, of whom two had not undergone surgery when they had bled a few weeks earlier. Primary bleeding episodes subsided without surgery in 10 of 21 cases, but 3 of these 10 patients (30%) rebled massively. By contrast primary excisional surgery was followed by recurrent hemorrhage in only 1 of 11 cases (9%). These differences in mortality and in recurrent bleeding rates, although not statistically significant, seem to favor removal of diseased bowel at the time of the first episode of massive hemorrhage.**

SEVERE GASTROINTESTINAL HEMORRHAGE in Crohn's disease (CD), although not mentioned in the original description of the illness,[1] is not highly exceptional.[2,3] It occurs with approximately the same frequency in all CD cases as in ulcerative colitis (UC),[4-8] ranging in various series from 0%[9-11] to 6%.[12-16]

Therapeutic approaches to severe hemorrhage have differed between UC and CD because of the differing long-term outcomes in the two diseases. Colectomy is carried out more readily in UC with the prospect of permanent cure, while a more conservative posture has been adopted for CD because of its proclivity to postoperative recurrence. This study was undertaken to determine if such moderation in CD is safe and effective.

## Material and Methods

Between 1960 and 1986, 21 patients with Crohn's disease (CD) were treated at The Mount Sinai Hospital on at least one occasion because of acute severe lower gastrointestinal hemorrhage. The records of 20 patients were derived from a retrospective review of the hospital records of 1526 patients admitted with CD before 1985, a proportion of 1.3%. The 21st patient was admitted for the first time in May 1986. There were 4 patients with severe hemorrhage among 597 (0.7%) with regional enteritis (RE), 14 among 650 (2.2%) with ileocolitis (IC), and 3 among 279 (1.1%) with Crohn's colitis (CC).

Severe hemorrhage was defined as a lower gastrointestinal hemorrhage originating in diseased bowel and requiring at least four units of blood during an interval not exceeding 2 weeks.

The diagnosis of Crohn's disease was made by the usual clinical,[17] radiographic,[18] endoscopic,[19] and pathologic[20] criteria,[21-23] including 13 cases in which there were surgical specimens.

Twenty-four other patients with severe hemorrhage in Crohn's disease (RE, 10; IC, 6; CC, 8) were excluded from this study for one (or in four cases for two) of the following reasons: (a) the source of massive hemorrhage was duodenal ulcer confirmed by gastroscopy and/or surgery (8 patients);[11] (b) bleeding occurred within 4 to 8 days after surgery or following radiotherapy (3 patients); (c) acute rectal hemorrhage originated from diseased areas of the digestive tract but did not meet our criteria of severity (8

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patients); (c) more than four units of blood were given but blood loss was chronic rather than acute (3 patients); and (e) the episode of hemorrhage occurred outside this institution in patients later seen at The Mount Sinai Hospital for other reasons (6 patients).

Comparative statistics were carried out using the chi square test.

### Results (Table 1)

There were 21 patients with severe hemorrhage in CD, 11 men and 10 women, with a mean age of 28 years (range, 18 to 48 years; median, 27 years) at the time of the first bleeding episode. The mean duration of disease from onset to time of hemorrhage was 6 years (range, 7 weeks to 26 years; median, 5 years). There were 26 episodes of severe hemorrhage: 17 patients bled only once, three bled twice, and one bled three times. Severe bleeding was never the first manifestation of the disease.

Twelve patients had surgery on 13 separate occasions: 11 patients came to surgery during their first bleeding episode and 1 of the 11 required a second operation for recurrent bleeding; the 12th patient, whose first hemorrhage had been treated medically, underwent his first operation during a recurrent episode of bleeding. All patients had been treated with prednisone at some time during the course of their disease, but only 10 of 21 were on steroids at the time of the first hemorrhage. There were two patients with associated toxic megacolon. One patient in this series previously was reported in a review of 25 cases of severe hemorrhage in ulcerative colitis[7] because the correct diagnosis of CD was not established until 12 months after his bleeding episode.

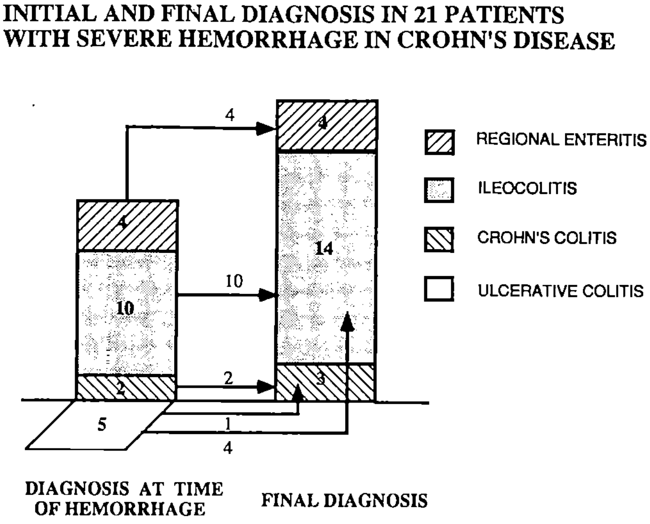

FIG. 1. Diagnoses of the 21 patients presenting with severe hemorrhage in Crohn's disease, distinguishing those 16 known to be suffering from CD at the time of initial bleeding from five originally diagnosed as having ulcerative colitis.

### *Differential Diagnosis and Site of Disease (Fig. 1)*

Sigmoidoscopy, radiology, or pathologic examinations of resected specimens performed at the time of the first severe hemorrhage established the diagnosis of CD in 16 patients (RE, 4; IC, 10; and CC, 2). In the 11 resections for primary hemorrhage, histopathology clearly revealed CD in seven patients (RE, 2; IC, 4; and CC, 1), but the initial pathologic diagnosis was UC in four patients. Ileocolitis was found in both patients with recurrent hemorrhage. Nine of the ten patients with ileocolitis had colonic involvement in continuity with diseased ileum and

TABLE 1. *Clinical and Epidemiologic Data of 21 Patients with Severe Hemorrhage in Crohn's Disease*

| Data | Male | Female | All Patients |
|---|---|---|---|
| Number of patients | 11 | 10 | 21 |
| Operated patients | 5 | 8 | 13 |
| Age at onset of disease (years) | | | |
| Median | 21 | 21 | 21 |
| Mean | 23.4 | 20.6 | 22.0 |
| Range | 14–41 | 14–38 | 14–41 |
| Age at time of first hemorrhage (years) | | | |
| Median | 28 | 25 | 27 |
| Mean | 29.5 | 26.5 | 28.0 |
| Range | 18–46 | 21–48 | 18–48 |
| Duration of disease from onset to hemorrhage (years) | | | |
| Median | 5 | 5 | 5 |
| Mean | 6.1 | 5.9 | 6.0 |
| Range | 7 wks–20 yrs | 8 wks–26 yrs | 7 wks–26 yrs |
| First/recurrent hemorrhage | 10*/3 | 10/1 | 20*/4 |
| Operated/recurrent hemorrhage | 5/1 | 8/0 | 13†/1 |
| Nonoperated recurrent hemorrhage | 5*/2 | 2/1 | 7*/4 |

* One male patient had massive bleeding previously elsewhere and was treated at Mount Sinai Hospital for the recurrent severe bleed.

† Includes two patients with recurrent hemorrhage and 11 with primary hemorrhage.

extending distally beyond the hepatic flexure (eight of these nine had extensive colitis sparing the rectum); the 10th patient had a normal ascending colon but skip lesions on the left side. For the five patients still labeled UC at the time of initial hemorrhage, the correct diagnosis of CD (CC, 1; IC, 4) was established 1 to 18 years later, following surgery (for 3), barium enema and sigmoidoscopy (for 1), or ileoscopy through ileostomy (for 1).

Among all 21 patients with severe hemorrhage, those four who had their inflammatory processes limited to the small bowel were derived from a population of 597 RE patients (0.7%), whereas the 17 with colonic involvement came from 929 IC + CC patients in the total series (1.9%). This higher proportion of cases of severe hemorrhage among the colitis and ileocolitis patients is significant by chi square analysis ($p < 0.001$) and remains so even after eliminating the five patients who were thought to have UC at the time of initial hemorrhage (12 of 924 or 1.3%; $p < 0.001$).

### *Blood Requirements*

Blood requirements either before operation or during the whole hospital course in nonoperated patients averaged 12.8 units (median, 8.5) per patient per admission. No significant differences were found between male and female patients, between operated and nonoperated patients, or between first and recurrent bleeding episodes. The length of hospital stay averaged 32 days (range, 8 to 115 days; median, 19 days): 33 days for a primary episode (range, 9 to 115 days; median, 21 days), and 28 days for recurrent bleeding (range, 8 to 74 days; median, 14 days).

### *Localization of Bleeding Point*

Celiac, superior, and inferior mesenteric angiography was performed on five occasions and revealed a bleeding site in only two patients, who underwent subsequent ileocolic resections. In both cases, the bleeding site was identified in the ileocecal area. In all other 19 cases, the precise bleeding site remained unknown but was presumed to have originated from one or more of the areas of inflammation. In fact even macroscopic examination of 13 resected specimens did not demonstrate an obvious bleeding point, except in the two instances of angiographically demonstrated ileocecal ulcerations.

### *Treatment (Fig. 2)*

Initial therapy at the time of primary or secondary hemorrhage consisted of blood transfusions and supportive measures, and the bleeding ceased spontaneously in

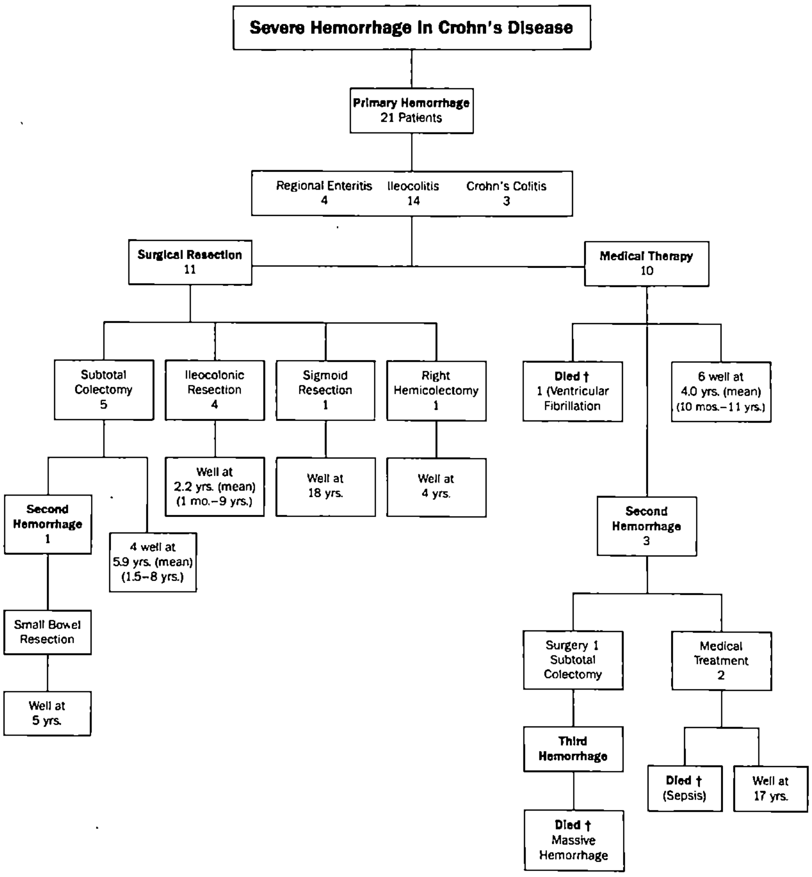

FIG. 2. Outcome of medical and surgical treatment of 26 episodes of severe hemorrhage in 21 patients with Crohn's disease. There was a higher rebleeding rate and a higher mortality rate in patients treated primarily medically.

12 of 25 instances (48%). Spontaneous cessation occurred with equal frequency during primary episodes (10 of 21 episodes, or 48%) and recurrences (2 of 4 recurrences, or 50%). One patient died during his third episode of massive bleeding before adequate therapy could be instituted. Twelve patients with persistent hemorrhage underwent surgery on 13 occasions, with an average interval between admission and operation of 7.6 days (range, 12 hours to 31 days; median, 3 days). All 11 patients operated on during their first bleeding episodes had colon resection: five subtotal colectomies (all but one with a mucous fistula plus ileostomy), one sigmoid resection, four ileocolic resections, and one right hemicolectomy. None had total proctocolectomy. The two patients with recurrent hemorrhage underwent a subtotal colectomy and a small bowel resection, respectively.

### *Follow-up*

*Mortality.* Three of the twenty-one patients in this series died. Only one death was directly attributable to exsanguinating hemorrhage. It occurred in a 25-year-old man with ileocolitis who had had two previous episodes of massive rectal hemorrhage, separated by one month, culminating in subtotal colectomy and ileostomy at The Mount Sinai Hospital. He died during a third massive bleeding episode while in another country 7 years later.

A second death occurred in a 40-year-old nonoperated woman who developed acute ventricular fibrillation 2 weeks after conservative treatment of a massive hemorrhage. The third death was a 27-year-old man who died 7 weeks after a recurrent massive hemorrhage and 4 days after surgery for perforation of the small bowel.

*Postoperative complications and duration of hospital stay.* Three of the eleven patients who were operated on for primary bleeding episodes developed serious postoperative complications. One patient with a postoperative fecal fistula followed by a pulmonary embolus was treated conservatively, while the other two required reoperation, one for a right subphrenic abscess and one for persistent rectal bleeding. Both of the patients who were operated on for a second hemorrhage had smooth postoperative courses, although one of them died during a third bleeding episode 7 years later (as described above).

*Late results.* Four of the twenty-one patients (19%) had recurrent massive hemorrhage from the small or large bowel, three at a mean of 22 months after nonoperative management, and one 10 months after a subtotal colectomy; the latter is doing well 5 years after a limited small bowel resection. A fifth patient, not counted among recurrent bleeders in this series, subsequently required surgery for massive hemorrhage from a documented duodenal ulcer.

## Discussion

Overt bleeding from the lower gastrointestinal tract has been reported to occur in Crohn's disease,[14,24–28] with a frequency as high as 45%.[15,29] The frequency of 'profuse rectal bleeding,' however, is only 2.5% to 6%[3,13] and it decreased to 1.4%[16] for hemorrhage so severe as to 'require blood transfusions to maintain normal vital signs.' The frequency in the present series, 20 patients of 1526, was 1.3%.

Although massive bleeding sometimes has been described as the initial manifestation of the disease,[3,12,30–34] this presentation was not observed in any of the cases in our series. Three of our patients, however, had relatively short disease durations of only 7 to 8 weeks before their first bleeding episodes. Hemorrhage tended to occur in patients with a slightly earlier age at onset of CD, 22 years compared to the overall mean of 26 years, in our series and others,[30,32,35] but the equal sex distribution we observed (M:F ratio, 11:10) is no different from that usually found among all cases of Crohn's disease.[32,18] As has been noted previously,[16] steroid therapy did not appear to be related to development of severe bleeding because 10 of our 21 patients were not on this form of therapy at the time of hemorrhage.

Characterization of severe hemorrhage in Crohn's disease is complicated by a number of factors: (a) the initial diagnosis is frequently incorrect (five cases diagnosed as UC at time of hemorrhage were ultimately found to have Crohn's disease (Fig. 1); (b) bleeding may occur from sources unrelated to CD (*e.g.*, eight patients with CD bled massively from a duodenal ulcer during the period of this study); and (c) the precise site of hemorrhage may be difficult to locate,[2,36–42] even after arteriography,[43] radionuclide scanning, or pathologic examination of resected specimens. Nonetheless we have identified a significantly higher frequency of severe hemorrhage in patients whose colons were involved (1.9%) than in those whose disease was confined to the small bowel alone (0.7%). This observation correlates with many reports,[3,15,23,37,44,45] although it contradicts one smaller series of seven severe bleeders in whom 'the incidence (sic) of bleeding approximated the distribution of disease for all patients.'[16]

The approach to management of severe hemorrhage depends on the physician's view of the propensity for recurrence. Conservative therapy sometimes has been advocated[34] in view of the possibility of spontaneous cessation of bleeding.[43] In the present series, spontaneous cessation occurred in 10 of 21 initial bleeding episodes. Nevertheless three of these patients (30%) rebled massively (one requiring surgical intervention), with two deaths. This outcome contrasts both with the low frequency of recurrent hemorrhage, 1 of 11 patients (9%), and with the high survival rate, 10 of 10 patients, following primary surgical resection. These differences, while not statistically significant, seem to favor removal of diseased bowel at the time of the first episode of massive bleeding.

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## References

1. Crohn BB, Ginzburg L, Oppenheimer GD. Regional enteritis. A pathologic and clinical entity. JAMA 1932; 99:1323–9132.
2. Fallis LS. Massive intestinal hemorrhage in regional enteritis. Report of a case. Am J Surg 1941; 53:512–513.
3. Rubin M, Lynwood Herrington J, Schneider R. Regional enteritis with major gastrointestinal hemorrhage as the initial manifestation. Arch Intern Med 1980; 140:217–219.
4. Block GE, Moossa AR, Simonowitz D, Hassan SZ. Emergency colectomy for inflammatory bowel disease. Surgery 1977; 82:531–536.
5. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. Gut 1964, 5:1–26.
6. Farmer RG. Clinical features and natural history of inflammatory bowel disease. Med Clin North Am 1980; 64:1103–1115.
7. Smith JN, Winship DH. Complications and extraintestinal problems in inflammatory bowel disease. Med Clin North Am 1980; 64: 1161–1171.
8. Robert JH, Sachar DB, Greenstein AJ. Management of severe hemorrhage in ulcerative colitis. Am J Surgery 1990; 159:550–555.
9. Eckel JH, Ogilvie JB. Regional enteritis. Am J Surg 1941; 53:345–348.
10. Warren R, Miller RH. Regional enteritis. N Engl J Med 1942; 228: 589–593.
11. Farmer RG, Hawk WA, Turnbull RB. Indication for surgery in Crohn's disease. Analysis of 500 cases. Gastroenterology 1976; 71:245–250.
12. Van Patter WN, Bargen JA, Dockerty MB, et al. Regional enteritis. Gastroenterology 1954; 26:347–450.
13. Daffner JE, Brown CH. Regional enteritis. I. Clinical aspects and diagnosis in 100 patients. Ann Intern Med 1958; 49:580–594.
14. Sparberg M, Kirsner JB. Recurrent hemorrhage in regional enteritis. Report of 3 cases. Am J Dig Dis 1966; 2:652–657.
15. Greenstein AJ, Kark AE, Dreiling DA. Crohn's disease of the colon. II. Controversial aspects of hemorrhage, anemia and rectal involvement in granulomatous disease involving the colon. Am J Gastroenterol 1975; 63:40–48.
16. Homan WP, Tang CK, Thorbjarnarson B. Acute massive hemorrhage from intestinal Crohn disease. Arch Surg 1976; 111:901–917.
17. Meyers S, Janowitz HD. Crohn's disease clinical features. *In* Bockus HL, Berk JE, Haubrich WS, Kalser M, Roth JLA, Vilardell F, eds. Gastroenterology. Philadelphia: WB Saunders, 1985, pp 2240–2259.
18. Marshak RH, Lindner AE. Radiologic diagnosis of chronic ulcerative colitis and Crohn's disease. *In* Kirsner JB, Shorter RG, eds. Inflammatory Bowel Disease, 2nd Edition. Philadelphia: Lea and Febiger, 1980, pp 341–409.
19. Waye J. The role of colonoscopy in the differential diagnosis of inflammatory bowel disease. Gastrointestinal Endosc 1977; 23: 150–154.
20. Whitehead A. Pathology of Crohn's disease. *In* Kirsner JB, Shorter RG, eds. Inflammatory Bowel Disease, 2nd Edition. Philadelphia, Lea and Febiger, 1980, pp 296–307
21. Lockhart-Mummery HE, Morson BC. Crohn's disease (regional enteritis) ofthe large intestine and its distinction from ulcerative colitis. Gut 1960; 1:87–105.
22. Cook MG, Dixon MS. An analysis of the reliability of detection and diagnostic value of various pathological features in Crohn's disease and ulcerative colitis. Gut 1973; 14:255–262.
23. Greenstein AJ, Geller SA, Dreiling DA, Aufses AH Jr. Crohn's disease of the colon. IV. Clinical features of Crohn's (ileo)colitis. Am J Gastroenterol 1975; 64:191–199.
24. Edwards H. Crohn's disease. An inquiry into its nature and consequences. Ann Roy Coll Surg (Engl) 1969; 44:121–139.
25. Krause U, Bergman L, Norlen BJ. Crohn's disease. A clinical study based on 186 patients. Scand J Gastroenterol 1971; 6:97–108.
26. Bandler M. Rectal bleeding in Crohn's disease of colon. NY State J Med 1972; 72:1585–1591.
27. Farmer RG. Clinical features and natural history of inflammatory bowel disease. Med Clin North Am 1980; 64:1103–1115.
28. Both H, Torp-Pedersen K, Kreiner S, et al. Clinical appearance at diagnosis of ulcerative colitis and Crohn's disease in a regional patient group. Scand J Gastroenterol 1983; 18:989–991.
29. Mekhjian HS, Switz DM, Melnyk CS, et al. Clinical features and natural history of Crohn's disease. Gastroenterology 1979; 77: 898–906.
30. Horwitz F, Baronofsky ID. Regional enteritis presenting as gross rectal bleeding. J Mt Sinai Hosp 1960; 27:19–22.
31. Corona FE, Dyck WP. Massive gastrointestinal hemorrhage as the sole clinical manifestation of regional enteritis (case report). Am J Dig Dis 1973; 18:1001–1004.
32. Sunkwa-Mills HNO. Life-threatening haemorrhage in Crohn's disease. Br J Surg 1974; 61:291–292.
33. Dent MT, Freeman AH, Dickinson RJ. Massive gastrointestinal bleeding in Crohn's disease. J R Soc Med 1985; 78:628–629.
34. Ciccarelli O, Coley GM. Massive rectal bleeding in Crohn's colitis. Conn Med 1986; 50:301–303.
35. Greenstein AJ, Sachar DB, Smith H, et al. Patterns of neoplasia in Crohn's disease and ulcerative colitis. Cancer 1980; 46:403–407.
36. Brown PW. Massive recurring bleeding in regional enteritis. Minn Med 1957; 40:847–848.
37. Goldberg SL, Frable MA. Massive intestinal hemorrhage in regional enteritis. Surgery 1963; 53:612–615.
38. Gerami S, Easley GW, Azer MS, Mendoza CB. Massive gastrointestinal hemorrhage due to regional enteritis (case report and brief review of the literature). W Va Med J 1970; 66:185–186.
39. Bersis AG, Koukoulas AG, Kalmandis AK. Acute regional enteritis. Intern Surgery 1976; 61:293–294.
40. Harvey JC, Rotstein L, Steinhardt M, et al. Massive lower gastrointestinal bleeding: an unusual complication of Crohn's disease. Can J Surg 1978; 21:444–445.
41. Podolny GA. Crohn's disease presenting with massive lower gastrointestinal hemorrhage. Am J Roentgenol 1978; 130:368–370.
42. Renison DM, Forouhar FA, Levine JB, Breiter JR. Filiform polyposis of the colon presenting as massive hemorrhage: an uncommon complication of Crohn's disease. Am J Gastroenterol 1983; 78: 413–416.
43. Bruyns E, Lubbers EJC, van Tongeren JHM. Major hemorrhage in Crohn's disease. Neth J Med 1979; 22:67–71.
44. Sauter KE. Massive gastrointestinal hemorrhage due to regional enteritis. Am J Surg 1966; 112:91–93.
45. Farmer RG, Hawk WA, Turnbull RB. Clinical patterns in Crohn's disease: a statistical study of 615 cases. Gastroenterology 1975; 68:627–635.

# Indications for Computed Tomography in Children with Blunt Abdominal Trauma

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**This investigation was undertaken to identify clinical variables, alone or in combination, that could be used to assign children to high- and low-risk categories for intra-abdominal injury following blunt trauma. Six hundred consecutive children who were examined with computed tomography (CT) following blunt trauma were enrolled. Complete data sets were available on 375 children. Stepwise logistic regression was used to identify predictor variables for the presence of abdominal injury. There were 174 children with abdominal injury detected by CT. Of these, 95 were classified as having significant injury. Indicators associated with significantly higher risk of abdominal injury included the following: more than three clinical indications given (odds likelihood ratio [OLR] = 4.60, 95% confidence interval [95% CI] = 2.29, 9.21, $p < 0.001$); gross hematuria (OLR = 5.80, 95% CI = 2.51, 13.4, $p < 0.001$); lap belt injury (OLR = 12.2, 95% CI = 2.22, 66.8, $p < 0.01$); assault or abuse as the mechanism of injury (OLR = 5.08, 95% CI = 1.07, 24.2, $p < 0.05$); abdominal tenderness (OLR = 2.73, 95% CI = 1.296, 5.82, $p < 0.01$); and Trauma Score ≤12 (OLR = 2.27, 95% CI = 1.006, 5.13, $p < 0.01$). No child with asymptomatic hematuria ($n = 56$), regardless of grade or neurologic impairment in the absence of abdominal findings ($n = 15$), had an abnormal CT examination. These data are useful as an adjunct to clinical judgment in triage when the availability of CT equipment is limited or there are competing extra-abdominal injuries.**

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COMPUTED TOMOGRAPHY (CT) HAS become the preferred method for the imaging evaluation of children following blunt trauma to the trunk.[1-3] Yet there is considerable debate regarding the indications for CT examination and which children are at high risk for having an intra-abdominal injury.[4-7] Because children often cannot verbalize symptoms and localization of pain is difficult, most centers use the CT scan to detect significant intra-abdominal injuries. Hemodynamic stability and absence of extra-abdominal life-threatening injuries are requirements commonly used in the selection of children for CT examination. Nevertheless high-yield indications for obtaining a CT examination have not been well defined. This paper evaluates common indications for abdominal CT in injured children and attempts to establish criteria for the use of abdominal CT.

## Materials and Methods

We reviewed the clinical data and CT examinations of 600 consecutive children who were evaluated with CT after blunt abdominal trauma at The Children's National Medical Center in Washington, D.C. between January 1983 and February 1989. Children who were clinically suspected of having injury to intra-abdominal organs and who were hemodynamically stable after initial resuscitation underwent CT evaluation.[2] Computed tomography scans were performed on a GE 9800 CT scanner (General Electric, Milwaukee, WI) with 10-mm sections at 1-cm intervals. All children received 3 mL/kg of iothalamate 43% (Conray Mallincrodt, St. Louis, MO) by rapid intravenous infusion for contrast enhancement. Gastrointestinal contrast was not used routinely.

### *Data Collection*

The referring surgeon completed a data sheet at the time of initial CT consultation. Information included demographic data, Trauma Score, Glasgow Coma Score, blood pressure at time of arrival at the CT scanner, as well as clinical indications for CT examination. Indications for CT examination included the presence of abdominal signs and symptoms such as abrasions, contu-

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sions, ecchymoses, distension, absence of bowel sounds, tenderness, presence of blood per rectum or in the stomach by nasogastric tube, presence and degree of hematuria, dropping or low hematocrit ($\leq$30%), and neurologic impairment, such that physical examination of the abdomen was considered unreliable.

The total number of clinical indications given by the referring surgeon for each child was tabulated and used as a variable in subsequent analyses. The type of management (operative or nonoperative), overall hospital course, and clinical outcome were recorded at the time of discharge.

### *Classification of Injuries by CT*

Computed tomography examinations were divided into two categories for analysis: normal to minor injury and significant injury.[8] Computed tomography findings such as a small amount of peritoneal fluid, small solid organ contusions, and nondisplaced pelvic ramus fractures were categorized as minor findings because their presence would not significantly influence clinical management, or were visible on preliminary radiographs (nondisplaced pelvic fractures) and thus did not require CT for identification. All remaining injuries (hematoma, laceration of a solid organ, hollow organ perforation, moderate and large hemoperitoneum, displaced or complex pelvic fracture, and vertebral fracture or dislocation) were categorized as significant abdominal injuries (SAI).

### *Data Analysis*

Stepwise logistic regression was used to identify predictors for significant abdominal trauma. In this model, a patient can have $k$ possible signs or symptoms ($s_1$, $s_2$, $s_3$ . . . . . , $s_k$), where $sj = 1$ denotes the presence of the $j$th sign or symptom and $sj = 0$ denotes its absence. The probability p that the patient has the condition can be derived from the following model[9]

$$\log [p/(1 - p)] = \beta_0 + \beta_1 s_1 + \ldots\ldots. \beta_k s_k.$$

This equation states that the logarithm of the odds of the diseased state to the normal state is a linear function of the symptoms, where $\beta j$s are weighted coefficients for the various symptoms. A symptom $sj$ will be relatively influential if its coefficient $\beta j$ is large, and relatively unimportant if $\beta j$ is close to zero. This model is analogous to a linear regression model in which an outcome (dependent) variable is expressed as a linear function of a regressor (independent) variable. Beginning with a constant model, at each step, a variable was entered into the equation in order of importance if its addition improved the model with a p value of $\leq$0.1. Variables not satisfying entry criteria were not included. In addition to individual variables, combinations of certain variables were submitted to the model to evaluate the possible interaction between clinically related variables. These interactions included hematuria and pelvic fracture, abdominal distension, tenderness, and Trauma Score; Trauma Score and number of indications, and abdominal tenderness; abdominal distension and tenderness, abrasions/contusions, absent bowel sounds, and Trauma Score.

In addition to the multivariate analyses, each variable was analyzed separately. Differences in means between two groups with continuous variables were analyzed by t test where appropriate. Differences in means among groups with interval level data such as Trauma Score were analyzed using nonparametric statistics (Mann-Whitney U test for two group comparisons). Differences in proportion between groups were analyzed by contingency table analysis, with confirmation by a Pearson chi square statistic. All univariate tests were two tailed and significance was considered at $p \leq 0.05$.

## Results

### *Patient Population*

Six hundred children were examined consecutively with CT following blunt trauma. There were 385 boys and 215 girls. Their ages ranged between 1 month to 18 years (mean age, 7.8 years). Ten children who were hemodynamically unstable and had signs of serious intra-abdominal injury underwent laparotomy without CT evaluation. The mechanisms of injury reflected the urban setting of the Children's National Medical Center. Four hundred fifty-four children (76%) were injured as a result of a motor vehicle crash (291 pedestrians, 163 passengers). A subset of 15 children (9.2%) who were passengers were classified as having lap belt injuries. Children were considered to have a lap belt injury if they were wearing a lap-style restraint only while a passenger in a motor vehicle crash and had a characteristic linear bruise or contusion across the lower abdomen or pelvis.[10] Eighty (13%) were injured in falls, 28 (5%) as result of assault, and 20 (3.2%) in bicycle accidents. Ten children (1.6%) were injured by other mechanisms such as sledding, skiing, falling objects, and sports; in 8 children (1.2%), the mechanism of injury was not known.

### *Abdominal Injuries*

One hundred seventy-four children (29%) had abdominal injuries detected by CT. Of these, 95 (54.6%) were classified as significant. The number and location of these injuries are described in Table 1. There were no significant differences in age, gender, or mechanism of injury between children with significant injury *versus* minor, or no abdominal injury. Table 2 shows the frequency of each clinical indication in the study population.

TABLE 1. *Number and Location of Injuries in 174 Children*

| Organ Injured | Number |
|---|---|
| Spleen | 40 |
| Liver | 37 |
| Kidney | 27 |
| Pancreas | 7 |
| Bladder | 3 |
| Bowel | 8 |
| Spine | 4 |
| Bony pelvis | 1 |

TABLE 3. *Comparison of Clinical Variables in Patients with Missing Data* Versus *Patients with Complete Data Sets*

| Variable | % Patients with Missing Data (n = 225) | % Patients with Complete Data Sets (n = 375) | p Value‡ |
|---|---|---|---|
| Significant abdominal injury | 14.7 | 16 | 0.74 |
| Male gender | 64.1 | 64.8 | 0.86 |
| Need for surgery | 4.0 | 3.5 | 0.73 |
| Mortality | 1.8 | 5.4 | 0.049 |
| Mean TS* | 14.39 | 13.28 | 0.0004 |
| Mean GCS† | 13.17 | 11.64 | 0.0002 |
| Age (years) | 8.05 | 7.65 | 0.299 |

* Trauma Score.

† Glasgow Coma Score.

‡ Significance tested by Pearson chi square, t-test or Mann-Whitney U test as appropriate.

## *Indications for CT Examination: Multivariate Analysis*

Logistic regression was performed on a subset of 375 children in whom complete data sets were available. To ensure that this sample was representative of the entire population, we compared this group with the group of patients with missing data elements (Table 3). There were no significant differences in frequency of SAI, gender, need for laparotomy, or age. Children with missing data elements had significantly higher (less severe) Trauma and Glasgow Coma Scores, and a lower mortality rate ($p < 0.05$).

Number of clinical indications was the first parameter to enter in the logistic regression model, with p value $< 0.001$ (Table 4). At the second step, gross hematuria added the most additional information in categorizing SAI ($p < 0.001$). Mechanism of injury entered in the third step. In this analysis, the risk of SAI for other mechanisms of injury was compared relative to the risk associated with motor vehicle-related accidents. Two mechanisms of injury were associated with a significantly higher risk of SAI. Children who were scanned as a result of a lap belt injury or abuse or assault were 12.2 times and 5.08 times as likely to have SAI than those children scanned as a result of motor vehicle crashes, respectively ($p < 0.01$ and $< 0.05$, respectively). Abdominal tenderness entered in step number four ($p < 0.01$). The final variable to add any information to the model was Trauma Score $\leq 12$ with a p value of $< 0.01$. No additional variables met the entrance criteria of $p < 0.10$. Therefore none of the other individual variables or interactions of variables added any information over and above that provided by the five variables: number of indications $\geq 4$, gross hematuria, mechanism of injury, abdominal tenderness, and Trauma Score $\leq 12$.

Table 5 shows the results of the univariate analyses of association between each variable and the presence of SAI separately. These analyses were performed to evaluate the relationship of individual variables with SAI confirming each variable's importance in relation to the multivariate analysis. Therefore we did not correct the significance criteria for multiple comparisons. The multivariate logistic regression did not include several variables that may have been associated with a high frequency of SAI because of multicollinearity (independent variables that are highly correlated). For example, variables such as Trauma Score and Glasgow Coma Score were highly correlated with each other such that only Trauma Score entered into the logistic regression model. The presence of several abdominal signs also were correlated significantly with SAI in this univariate analysis. Of these, only abdominal tenderness was allowed to enter into the multivariate model. The remaining signs (abdominal abrasions or contusions, distension, absent bowel sounds, blood per NG tube or per rectum, and emesis) were excluded because they did not contribute additional information. Although the presence of gross hematuria, or a Glasgow Coma Score of $\leq 8$ were significantly associated with SAI, this appeared to be true only if other clinical indications were present. No child with either gross hematuria or a Glasgow Coma Score of

TABLE 2. *Type and Frequency of Clinical Indications for Abdominal CT*

| Variable | Number of Patients with Variable Present | % Patients with Variable Present |
|---|---|---|
| Hematuria | 371 | 61.9 |
| Dipstick only | 88 | 14.7 |
| Microscopic | 226 | 37.7 |
| Gross | 57 | 9.5 |
| Abdominal tenderness | 263 | 44.1 |
| Neurologic obtundation | 220 | 36.9 |
| Abdominal abrasions/ contusions | 178 | 29.8 |
| Bowel sounds absent | 146 | 24.5 |
| Low or dropping hematocrit | 99 | 24.3 |
| Abdominal distension | 132 | 22.1 |
| Blood per nasogastric tube | 62 | 10.4 |
| Emesis | 56 | 9.4 |
| Pelvic fracture | 44 | 7.4 |
| Chest trauma | 38 | 6.3 |
| Blood per rectum | 29 | 4.9 |

TABLE 4. *Clinical Variables Associated with Increased Risk for Significant Abdominal Injury by Multivariate Analysis*†

| Step | Variable | Odds Ratio | 95% CI* | p Value | Coefficient ($\beta$) | SE‡ |
|---|---|---|---|---|---|---|
| 1 | ≥4 Clinical indications | 4.6 | 2.29, 9.21 | <0.001 | 1.525 | 0.353 |
| 2 | Gross hematuria | 5.8 | 2.51, 13.4 | <0.001 | 1.757 | 0.425 |
|  | Mechanism of Injury§ |  |  |  |  |  |
| 3 | 0 Motor vehicle accident | 1 |  |  | 0.0 |  |
|  | 1 Lap belt injury | 12.2 | 2.22, 66.8 | <0.01 | 2.500 | 0.866 |
|  | 2 Bicycle | 0.702 | 0.21, 2.35 | NS | −0.354 | 0.614 |
|  | 3 Fall | 1.78 | 0.46, 6.84 | NS | 0.579 | 0.683 |
|  | 4 Abuse/assault | 5.08 | 1.07, 24.20 | <0.05 | 1.626 | 0.729 |
|  | 5 Other | 4.20 | 0.96, 18.30 | NS | 1.436 | 0.748 |
| 4 | Abdominal tenderness | 2.73 | 1.29, 5.82 | <0.01 | 1.006 | 0.384 |
| 5 | Trauma score ≤12 | 2.27 | 1.00, 5.13 | <0.01 | 0.819 | 0.415 |
| Constant |  |  |  |  | −5.3952 | 1.1850 |

* 95% Confidence Intervals = $[e^{\text{coeff.} \pm 1.96\,(\text{s.e.})}]$.
† Stepwise logistic regression analysis.
‡ Standard error.
§ Odds likelihood ratio for mechanism of injury was computed by comparing motor vehicle accidents to all other mechanisms of injury.
NS, not significant.

≤8 as the only clinical indication for CT examination had abnormal findings on CT.

Based on these results, we undertook a more indepth exploratory analysis using data from the entire study population (n = 600).

*Number of Clinical Indications*

Figure 1 shows the distribution of the number of clinical indications given by the referring surgeon and the proportion of children with SAI by number of clinical indications. Children who had many indications (more than three per child) occurred infrequently but were more likely to have SAI, as well as injury to more than one abdominal organ and were more likely to require laparotomy ($p < 0.0001$ for all three outcomes by chi square). The most common indications in children with SAI and ≤3 indications given (n = 57) were hematuria (53%), abdominal tenderness (49%), abdominal abrasions or contusions (26%), and neurologic impairment (22%). Only 7 of 145 children (4.8%) with one clinical indication given had SAI. Of these five had abdominal tenderness, one had emesis, and one had a nondisplaced pelvic fracture detected on plain radiographs.

TABLE 5. *Clinical Variables Associated with Increased Risk for Significant Abdominal Injury by Univariate Analysis*

| Variable | p Value† |
|---|---|
| Gender | NS |
| Mechanism of injury | NS |
| Trauma score ≤ 12 | 0.0371 |
| Glasgow coma score ≤ 8 | 0.0523 |
| Neurological impairment | NS |
| Abdominal tenderness | 0.0029 |
| Abdominal abrasions/contusions | 0.0308 |
| Abdominal distension | 0.0002 |
| Absent bowel sounds | 0.0005 |
| Blood per nasogastric tube | 0.0206 |
| Blood per rectum | NS |
| Emesis | NS |
| Fractured pelvis* | 0.0269 |
| Gross hematuria | 0.0001 |
| Chest trauma‡ | 0.0040 |
| Number of clinical indications ≥ 4 | 0.0001 |
| Hematocrit < 25% | 0.027 |
| Gross hematuria (only sign) | NS |
| Glasgow coma score ≤8 (only sign) | NS |

† Significance tested by Pearson chi square statistic. NS, not significant (p > 0.05)
* Pelvic fracture identified on plain radiographs.
‡ Chest trauma defined as the presence of thoracic abrasions/contusions on physical examination and/or rib, spine fracture, hemo, pneumothorax, parenchymal opacification, or hematoma on initial plain radiograph of the chest.

*Gross Hematuria*

Gross hematuria was present in 57 children (9.5%), and microscopic- or dipstick-positive hematuria was detected in 312 (52%). Thirty-nine per cent of children with gross hematuria had SAI, compared to 12.8% of children with lesser grades of hematuria, and 13.4% of children with no blood detected in the urine ($p < 0.0001$ by chi square). Lesser grades of hematuria did not appear to be associated with a significant increase in risk of SAI. Gross hematuria was not only a marker of injury to the urinary tract but also was an indicator of nonurinary injury. Of 22 children with SAI and gross hematuria, 11 had injury to more than one abdominal organ, and 10 had no detectable anatomic injury to the urinary tract but had injuries to the spleen (6), liver (4), pancreas (1), and bowel (1). No child who had only asymptomatic hematuria (n = 56), regardless of grade, had an abnormal CT.

*Abdominal Tenderness*

Of the six abdominal signs and symptoms recorded in this study, abdominal tenderness was the only one to enter

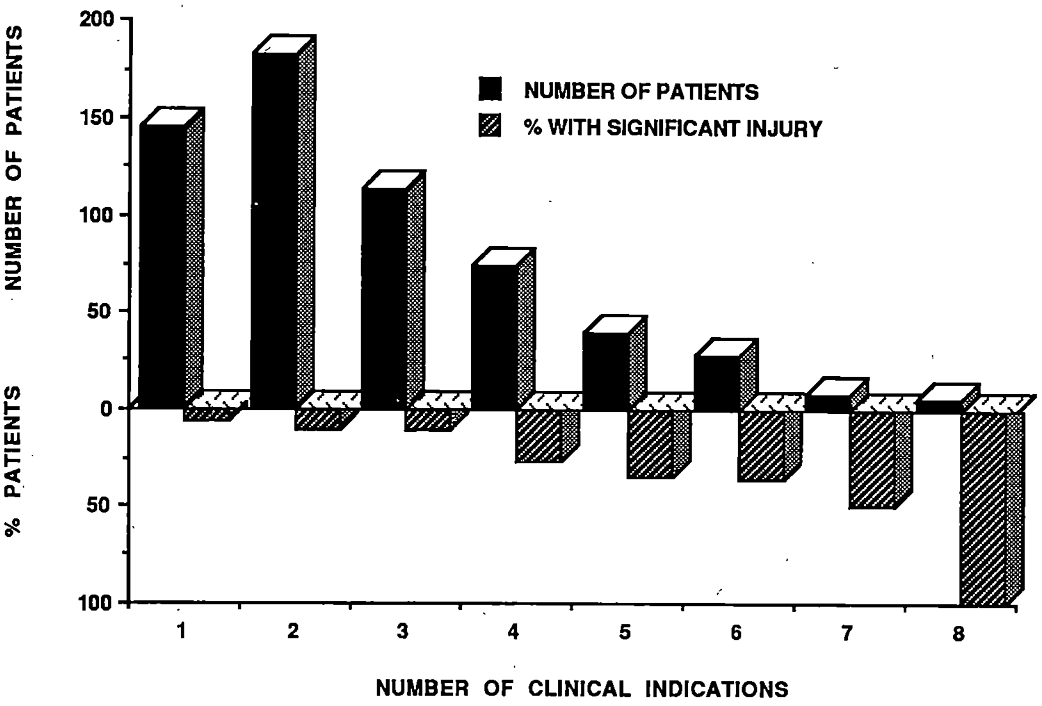

FIG. 1. Frequency distribution of the number of clinical indications given by the referring surgeon, and proportion of children with significant abdominal injury by number of clinical indications.

as a significant variable in the logistic regression analysis. Twenty-two per cent of children with abdominal tenderness had SAI, compared to 9.9% of children without this symptom ($p < 0.0001$ by chi square). Interestingly abdominal tenderness was present in 44% of all children studied and could be elicited in 29% of children 2 years or younger and in 14% of children with a Glasgow Coma Score of ≤8.

### *Trauma Score*

Figure 2 shows the distribution of Trauma Scores in the study population and the frequency of SAI by Trauma Score. Although the presentation of children with low Trauma Scores (≤12) was relatively infrequent, they were at higher risk for SAI ($p = 0.03$ by chi square). The lower the Trauma Score, the higher the proportion of children with SAI.

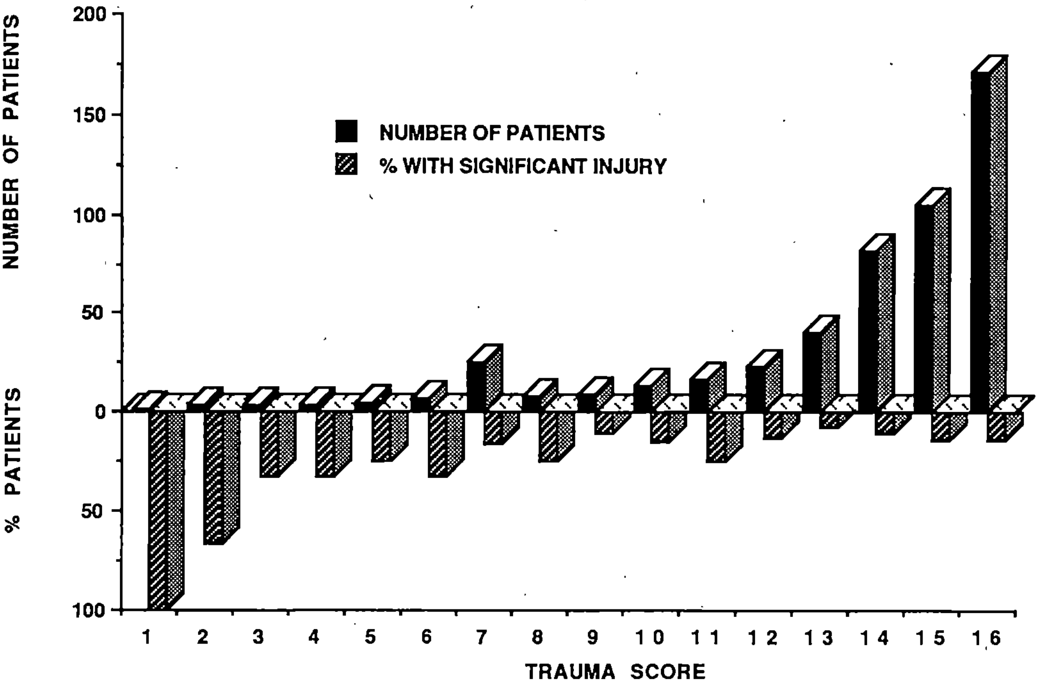

FIG. 2. Frequency distribution of trauma scores in the study population, and proportion of children with significant abdominal injury by trauma score.

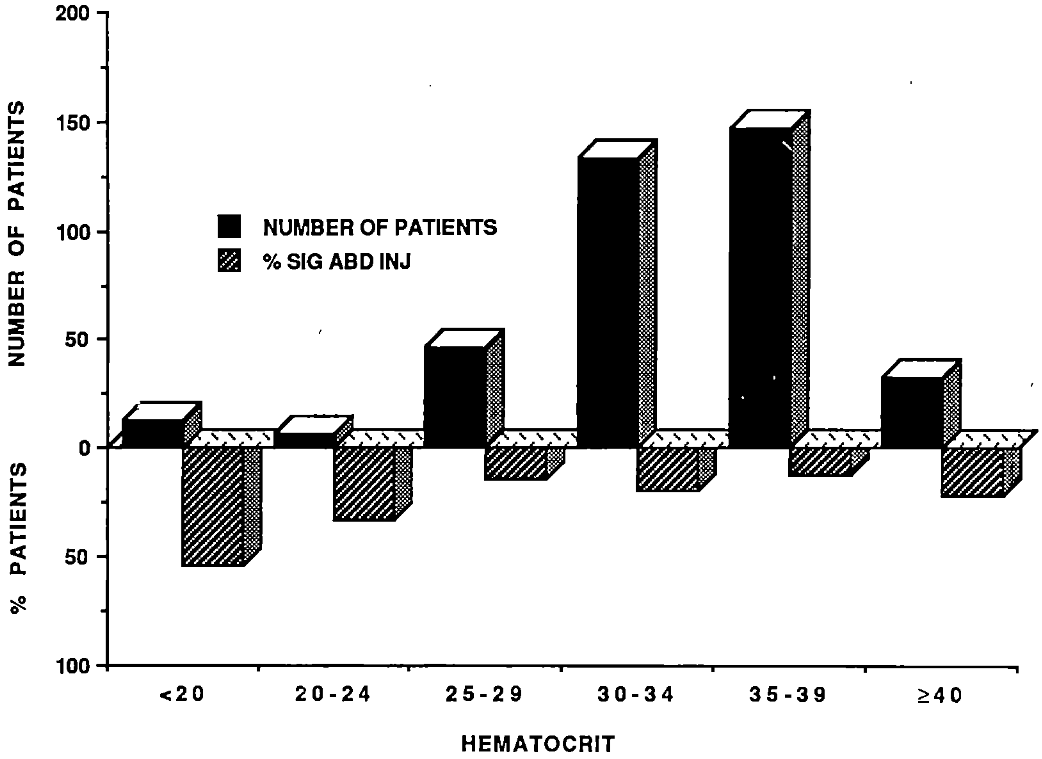

FIG. 3. Frequency distribution of hematocrit values and proportion of children with significant abdominal injury by hematocrit.

*Hematocrit*

The distribution of hematocrit values and the proportion of patients with SAI are shown in Figure 3. At a hematocrit level less than 30%, decreasing hematocrit was associated with increasing risk of SAI ($p < 0.009$ by chi square).

### Discussion

If clinical examination could predict accurately which children had abdominal injuries and the nature of those injuries, there would be no need for additional diagnostic tests such as abdominal CT or peritoneal lavage. Management could be based on the presence or absence of clinical criteria alone. Our goal was to identify specific individual or combinations of clinical indicators that would differentiate children at high-risk of underlying abdominal injuries from those at minimal or low-risk.

This study shows that the presence of the following variables is associated with a significantly higher risk of abdominal injury:

- More than three clinical indications
- Gross hematuria
- Lap belt injury
- Assault or abuse as the mechanism of injury
- Abdominal tenderness
- Trauma Score ≤12.

Of the seven specific signs relating to the abdomen, only gross hematuria and abdominal tenderness entered as significant variables in the logistic model. Although other abdominal signs such as abdominal distention, absent bowel sounds, blood per nasogastric tube, and abdominal abrasions or contusions were associated significantly with SAI on contingency table analyses, in the presence of tenderness or gross hematuria they did not contribute any additional information.

Aside from the expected increase in injuries to the urinary tract, children with gross hematuria also had a higher frequency of nonurinary injuries. This suggests that direct trauma to the abdomen may be absorbed differently by different organs, depending on their location and relative size. For example the force of a blow to the left upper quadrant may be unequally shared by the spleen and the relatively unprotected left kidney, resulting in variable anatomic injury to the spleen and sufficient capillary disruption in the kidney to result in gross hematuria without detectable anatomic injury on CT. Children with lesser grades of hematuria were not at any higher risk for abdominal injury than those with no blood detected in the urine. This is in contrast to our previous study of 378 children in which we detected a small but significant difference in frequency of abdominal injury in children with dipstick-positive or microscopic hematuria.[6]

It is not surprising that lower Trauma Score values were associated with a higher risk for SAI. The Trauma Score has been used extensively in both adult and pediatric trauma populations as an assessment of physiologic derangement and is highly correlated with outcome.[11,12] However using this score alone as an indicator of abdominal injury would be difficult because of the many causes for physiologic derangement that can be present in a child with multisystem injury. Similarly low hematocrit is a time-honored but nonspecific indicator of blood loss. Although lower hematocrit values (less than 25%) were associated with a higher frequency of SAI on univariate analyses, this variable was not strong enough as a predictor to enter into the logistic regression model. Furthermore evaluating the significance of a low or borderline hematocrit level in children is more difficult because children tend to have a lower hematocrit level than adults, even in the teenage years.[13]

In addition to clinical and laboratory signs that place the injured child at high risk for SAI, our data confirm previous findings regarding low-risk indicators for abdominal CT.[4,6] No child with asymptomatic hematuria (n = 56), regardless of grade or neurologic impairment in the absence of abdominal findings (n = 15), had an abnormal CT examination.

Few reports exist about clinical and laboratory indications for abdominal CT in children. Haftel et al[7] used univariate techniques to study 90 consecutive children with blunt trauma. They found a significant association between the presence of gross hematuria, absence of bowel sounds, amylasemia, and metabolic acidosis and an abnormal CT scan. The presence of neurologic impairment is used as an indication for abdominal CT examination. Beaver and colleagues[5] performed abdominal CT examinations in children with major head injuries, even when no abdominal signs of underlying injury were present on physical examination. They found that 15 of 65 children (23%) with a Glasgow Coma Score less than 10 had abdominal injuries and that abdominal signs in this group are unreliable indicators of underlying abdominal injury. In contrast a previous study also found that neurologically impaired children (Glasgow Coma Score less than 8) who had signs referable to the abdomen had a higher frequency of abdominal injury, injury to multiple abdominal organs, and combined chest and abdominal injuries.[4] However every child with abdominal injury on CT scan had specific abdominal signs indicative of underlying injury.

The variable with the strongest association with SAI was the number of clinical indications present at initial evaluation. Significant abdominal injury was infrequent in children with few clinical signs and common in children with many (more than three) indications. This suggests that specific abdominal or laboratory signs may not be as important as the overall clinical impression in predicting the presence of underlying injury.

Two mechanisms of injury were associated with a higher risk of SAI: lap belt injuries and assault or abuse. Although relatively infrequent in occurrence (approximately 3% of all children examined with CT), lap belt injuries are associated with a high risk for injury to the spine, bowel, and bladder.[14] Battered children with visceral injuries appear to represent a select population with severe injury. As detailed in a separate report, these children had significantly lower trauma score (8.3 *versus* 12.2) and a higher mortality rate (50% *versus* 14.5%) than battered children without visceral injury.[15]

We conclude that there are certain combinations of clinical and laboratory observations that are useful in triage of children into high- and low-risk categories for significant abdominal injury and that these data are useful as an adjunct to decision making when limited availability of CT equipment or competing extra-abdominal injuries exist. Children who manifest any one of the following are at high risk for significant abdominal injury: more than three clinical indications, gross hematuria, lap belt injury, or assault/abuse as mechanisms of injury, abdominal tenderness, and Trauma Score $\leq 12$. These children require thorough examination with CT.

## References

1. Kaufman RA, Towbin R, Babcock DS, et al. Upper abdominal trauma in children: imaging evaluation. AJR 1984; 142:449–460.
2. Taylor GA, Fallat ME, Potter BM, Eichelberger MR. The role of computed tomography in blunt abdominal trauma in children. J Trauma 1988; 28:1660–1664.
3. Siegel MJ, Balfe DM. Blunt renal and ureteral trauma in childhood: CT patterns of fluid collections. AJR 1989; 152:1043–1047.
4. Taylor GA, Eichelberger MR. Abdominal CT in children with neurologic impairment following blunt trauma. Ann Surg 1989; 210: 229–233.
5. Beaver BL, Colombani PM, Fal A, et al. The efficacy of computed tomography in evaluating abdominal injuries in children with major head trauma. J Pediatr Surg 1987; 22:1117–1122.
6. Taylor GA, Eichelberger MR, Potter BM. Hematuria a marker of abdominal injury in children after blunt trauma. Ann Surg 1988; 208:688–693.
7. Haftel AJ, Lev R, Mahour GH, et al. Abdominal CT scanning in pediatric blunt trauma. Ann Emerg Med 1988; 17:684–689.
8. Brick SH, Taylor GA, Potter BM, Eichelberger MR. Hepatic and splenic injury in children: role of CT in the decision for laparotomy. Radiology 1987; 165:643–646.
9. Wijesinha A, Begg CB, Funkenstein HH, McNeil BJ. Methodology for the differential diagnosis of a complex data set. Med Decis Making 1983; 3:133–154.
10. Taylor GA, Eggli KD. Lap belt injuries of the lumbar spine in children: a pitfall in CT diagnosis. AJR 1988; 150:1355–1358.
11. Champion HR, Sacco WJ, Hunt TK. Trauma severity scoring to predict mortality. World J Surg 1983; 7:4–11.
12. Eichelberger MR, Mangubat EA, Sacco WS, et al. Comparative outcomes of children and adults suffering blunt trauma. J Trauma 1988; 28:430–434.
13. Committee on Iron Deficiency, AMA. Iron deficiency in the United States. JAMA 1968; 203:407.
14. Sivit CJ, Taylor GA, Newman KD, et al. Seat-belt injuries in children: the lap belt complex. Presented at the 33rd Annual Meeting of The Society for Pediatric Radiology, Cincinnati, Ohio, April, 1990.
15. Sivit CJ, Taylor GA, Eichelberger MR. Visceral injury in battered children: a changing perspective. Radiology 1989; 173:659–661.

# Mitomycin C as an Adjuvant Treatment to Resected Gastric Cancer

## *A 10-year Follow-up*

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**Seventy consecutive patients were entered in a two-arm randomized trial after surgical resection for locally advanced gastric cancer. In the first arm, 37 patients were included as a control group, receiving no further treatment after surgery. In the second arm, 33 patients were treated with adjuvant chemotherapy consisting of mitomycin C (MMC), 20 mg/m$^2$ administered intravenously once every 6 weeks for four consecutive cycles. All patients in both arms were followed in the same way for 5 years. At 5 years 23 of 37 patients in the control arm and 7 of 33 patients in the treatment arm were dead because of relapse. Actuarial survival curve was statistically significant in favor of patients given adjuvant MMC ($p < 0.001$). After 10 years follow-up, 31 of 37 patients in the control arm and 16 out of 33 patients in the treatment arm were dead because of relapse, the statistical differences continuing in the actuarial survival curve in favor of treated patients ($p < 0.01$). The best advantages of adjuvant treatment were observed in the T3N0M0 stage. The most frequent relapse site was the peritoneal cavity and the relapse pattern shows special decrease in liver metastases in treated patients. Toxicity was acute and mild. No delayed toxicity or second malignancies were observed. These data suggest that adjuvant MMC after resected surgery of gastric cancer is a successful treatment and its effects are still evident after 10 years of follow-up.**

IN 1983 WE PUBLISHED the results after 5 years of follow-up of 70 patients included in a randomized trial. Thirty-seven patients were followed with no further treatment after surgery as a control group, and 33 were treated with adjuvant mitomycin C (MMC) after surgery for locally advanced gastric cancer.[1]

At that time, actuarial survival was significantly better in the treated group than in the control one. The study was considered positive in favor of adjuvant treatment after resected surgery in gastric cancer. Other authors noted that adjuvant chemotherapy may include MMC, immediately after surgery or even just before surgery.[2] Until 1985 only two positive trials were published in the West: a trial of the Gastrointestinal Tumor Study Group and our own.[1,3] The other study of the Veteran's Administration Surgical Oncology Group was positive at the beginning but lost its statistical significance after 2 years of follow-up.[4] There is no report of the outcome in these patients after 5 years of follow-up. These facts induced us to report the results of long-term survival in our patients.

### Materials and Methods

Between 1975 and 1979, 70 patients were included in a two-arm randomized trial. All patients had histologically demonstrated gastric cancer, were 70 years old or younger, and had no other serious concomitant disease. Performance status were 0 or 1 of the Zubrob Scale.[5] Eligibility criteria included clinical stage T1N1 or N2, T2N0 or N1 or N2, T3N0 or N1, or N2 and M0. Stages T1N0 and T3N3 were excluded, the former because of its good prognosis only with surgery, and the latter because of the difficulties in resecting all of the tumor.

After surgical resection, patients were randomized into two arms: first a control arm of patients given no adjuvant chemotherapy, and second a therapeutic arm, treated with mitomycin C, 20 mg/m$^2$ administered once every 6 weeks. All patients were followed every 3 to 6 months during 5 years. In 1988 we reviewed the survival status of the group using the address and telephone data from the clinical chart. Actuarial survival curves were obtained according to Kaplan and Meier.[6] The survival probabilities of different groups were statistically compared by means of the log-rank test.[7]

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## Results

Patients' characteristics and TNM stages were homogenous in both groups (Table 1). Thirty-three patients were treated with adjuvant chemotherapy and 37 were included in the control arm. After 5 years of follow-up, 7 of 33 patients in the treatment group and 23 of 37 patients in the control arm were died because of relapse. The actuarial survival curve significantly favored the adjuvant treatment ($p < 0.001$). After 10 years of follow-up, 16 patients in the treatment group and 31 patients in the control one were dead because of relapse, the statistical significance persisting between both survival curves ($p < 0.001$) (Fig. 1). In the 5-year review of T3N0 and T3N1, the TNM stages obtained better advantages with adjuvant chemotherapy. At 10 years of follow-up in the T3N0 subgroup, 5 of 12 of the treated patients and 8 of 10 of the nontreated patients had died, the statistically significant differences persisting in favor of the former group ($p < 0.05$). In the T3N1 subgroup, 7 of 12 treated patients compared to 11 of 12 nontreated patients were dead, maintaining the statistical significance in favor of treated patients ($p < 0.025$).

Peritoneal relapses were observed in 13 patients of the treatment group and only three relapses were in the liver. In the control group, peritoneal relapses numbered 17 and hepatic metastases numbered 11. Comparing the relapse rate after 5 and 10 years, an increase was observed in peritoneal relapses of the treated group. Furthermore hepatic relapses increased from 3 to 11 cases. Comparison of relapse pattern at 5 and 10 years follow-up are specified in Table 2.

Toxicity was acute and mild, consisting in leukopenia, thrombopenia, nausea, and vomiting. No cases of MMC renal damage were observed. These data are already published.[1] After a long-term follow-up, no delayed toxicity or second malignancies were observed.

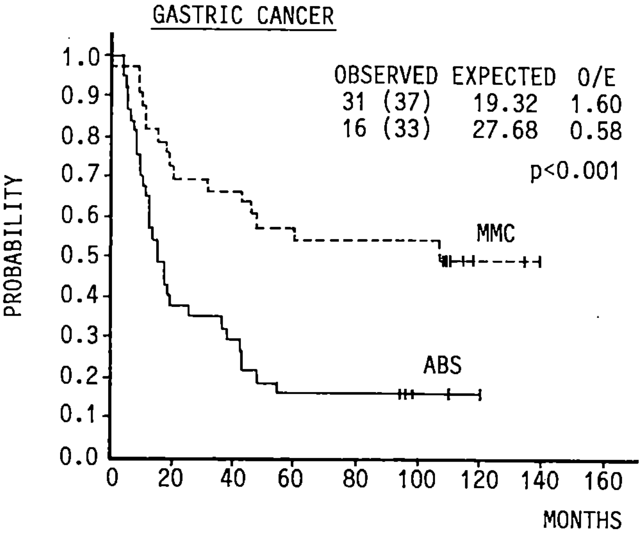

FIG. 1. Actuarial survival care at 10 years of follow-up for two arms, abstention group (ABS) *versus* mitomycin C group (MMC).

## Discussion

In light of these data, we observe that adjuvant chemotherapy is still successful after 10 years of follow-up. As far as we know, ours is the first positive study on adjuvant chemotherapy of gastric cancer with a follow-up of more than 5 years in the West. Nevertheless there seems to be experiences along the same line in Japan.[8]

TABLE 1. *Patients' Characteristics*

| Characteristic | Mitomycin C | Abstention |
|---|---|---|
| Number | 33 | 37 |
| Male/female | 18/15 | 22/15 |
| Age range (years) | 37–70 | 39/70 |
| Age mean (years) | 53.2 | 54.6 |
| TNM | | |
| $T_2$-No, $N_1$ | 3 | 6 |
| $T_3$No | 12 | 10 |
| $T_3N_1$ | 12 | 12 |
| $T_3N_2$ | 6 | 9 |
| Extent of Resection | | |
| Partial gastrectomy | 16 | 22 |
| Total gastrectomy | 17 | 15 |

The control group helps to demonstrate the outcome of resected gastric cancer after 10 years of follow-up. In both groups we can see a plateau in the actuarial survival curve (Fig. 1) observed after a period of 5 years. Therefore, and according to Frei,[9] after this survival period these patients should be considered cured of neoplasia. Figure 1 shows that the increase in relapses referring to survival after the 5-year follow-up occurs before the 5-year period. Japanese authors noted these early relapses, pointing out that most of them occur between 0.5 and 1.5 years after surgery.[10,11]

In our experience, patients at stages T3N0M0 and T3N1M0 benefit the most from adjuvant treatment, but the limited number of patients did not allow for further staging of subgroups in the study. Comparing recurrence patterns at 5 and 10 years, no great differences are observed in the group treated with MMC. Peritoneal relapses are still more frequent than hepatic metastases. This fact

TABLE 2. *Relapse Pattern Follow-up After 5 or 10 Years*

| | 5 Years | | 10 Years | |
|---|---|---|---|---|
| Follow-up | Mitomycin | Control | Mitomycin | Control |
| Local | | 3 | 1 | 3 |
| Peritoneal | 7 | 16 | 13 | 17 |
| Liver | | 3 | 3 | 11 |
| Bone | | 1 | | 1 |
| Brain | | 1 | 1 | |
| Skin | 1 | | 1 | |
| Ovary | | | | 1 |

suggests that intravenous chemotherapy protects mainly against distant metastases and is less successful protecting peritoneal cavity dissemination in tumors infiltrating all of the stomach wall. Consequently the same authors suggest adding chemotherapy *via* the intraperitoneal route.[2]

Another important fact is that we had no late toxicity, after 5 years of follow-up, neither hemolytic uremic syndrome[12] nor second malignancies. Hirono et al.[13] found that 22 of 7672 gastric remnant carcinomas (0.22%) were second malignancies. All of these patients were operated on for gastric cancer with adjuvant MMC and followed for a mean of 9.4 years. There were no relevant significant differences between patients treated with adjuvant chemotherapy, including MMC, compared to the control group with no further treatment. The same authors in another study[14] observed that only 235 of 10134 patients (2.32%) resected from gastric cancer has a second neoplasm in a different part of the body after a mean of 8.8 years follow-up. There were no significant differences between the treatment group compared to the control group in this study either.

In western countries the positive results of adjuvant chemotherapy in resected gastric cancer are regarded skeptically.[15] This may explain why most of the studies published after 1985 were performed in the Orient and are based mostly on MMC and 5-fluorouracil derivatives with or without immunochemotherapy.[16-20] Our study induces us to support the efficacy of adjuvant chemotherapy in resected cancer. As Douglas[2] noted, MMC should be used in high doses, starting during or immediately after surgery, and added as intraperitoneal treatment.

## References

1. Alcobendas F, Milla A, Estape J, et al. Mitomycin C as an adjuvant in resected gastric cancer. Ann Surg 1983:198:13–17.
2. Douglass HO. Gastric cancer: overview of current therapies. Sem Oncol 1985; 3(Suppl 4):57–62.
3. Gastrointestinal Tumor Study Group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. Cancer 1982; 49:1116–1122.
4. Higgeing GA, Amadeo JH, Smith DE, et al. Efficacy at prolonged intermitent therapy with combined 5-FU and methyl-CCNU following resection for gastric carcinoma. Cancer 1983; 52:1105–1112.
5. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 1973; 4:31–42.
6. Kaplan GL, Meier P. Nonparametric estimations from incomplete observations. Am Statist Assoc J 1958; 53:457–481.
7. Peto R, Pike MC. Conservation of the approximation (O.E)2/E in the log rank test for survival data or tumor incidence data. Biometrics 1973; 29:579–584.
8. Ichihashi H, Kondo T, Nakazato H. Clinical results of a randomized controlled trial on the effect of adjuvant immunochemotherapy using Esquion and Krestin in patients with curatively resected gastric cancer 7 year survival. Cooperative Study Group for Cancer Immunochemotherapy. Tokai Gastrointestinal Oncology Group. Gan to Kagaku Ryoho 1987; 14:2758–2766.
9. Frei E III. Curative cancer chemotherapy. Cancer Res 1985; 45: 6523–6537.
10. Kikuchi K, Kunii Y, Kikuchi S. The problems of postoperative adjuvant chemotherapy in gastric cancer. Gan to Kagaku Rycho 1987; 14:1136–1142.
11. Wilson RE. Survival considerations in gastric cancer. Sem Oncol 1985; 12(Suppl 4):63–68.
12. Lesesne JB, Chiazze L, Erikson B, et al. First analysis of 102 cases from a registry of cancer associated hemolytic uremic syndrome. Proc Am Soc Clin Oncol 1986; 5:82.
13. Hirono M, Niimoto M, Toge T, et al. A cohort study on second malignancies in gastrectomized patients with gastric cancer. II. Second malignancies in gastric remnant. Jpn J Surg 1986; 16: 344–350.
14. Hirono M, Niimoto M, Toge T, et al. A cohort study on second malignancies in gastrectomized patients with gastric cancer. I. Second malignancies other than cancer of the gastric remnant. Jpn J Surg 1986; 16:336–343.
15. Engstrom PF, Lavin PT, Douglas HO, Brunner K. Postoperative adjuvant 5-Flourouracil plus Methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group Study (EST 3275). Cancer 1985; 55:1868–1873.
16. Niimoto M, Hattori T, Tamada R, et al. Postoperative immunotherapy with mitomycin C, Tagafur (Futraful) and PSK for curatively resected cases of gastric cancer. *In* Taguchi T, Andrysek O, eds. New Trends in Cancer Chemotherapy with Mitomycin C. Tokyo: Excerpta Médica, 1987, pp 113–119.
17. Hattori T, Inokuchi K, Taguchi T, Abe O. Postoperative adjuvant chemotherapy for gastric cancer, the second report. Analysis of data on 2873 patients followed for five years. Jpn J Surg 1986; 16:175–180.
18. Koyama S, Ozaki A, Iwasaki Y, et al. Randomized controlled study of postoperative adjuvant immunotherapy with Nocardia Rubra cell wall (N-CWS) and Tegafur for gastric carcinoma. Cancer Immunol Immunother 1986; 22:148–154.
19. Inokuchi K. Prolonged survival of gastric cancer patients on specific adjuvant chemotherapy. Jpn J Surg 1984; 14:351–359.
20. Yoshida K, Inokuchi H, Kano K, et al. Results of surgical treatment of gastric cancer. Special reference to the pathological findings. Tohoku J Exp Med 1984; 144:57–62.

# The Potential Role of Postoperative Hepatic Artery Chemotherapy in Patients with High-risk Hepatomas

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**The relationship between operative findings of hepatoma and the postoperative prognosis was studied to clarify indications for adjuvant hepatic arterial chemotherapy after hepatectomy. The results of adjuvant hepatic arterial chemotherapy using 0.4 mg/kg of doxorubicin and 0.12 mg/kg of mitomycin C and infusion of 5-fluorouracil were reported. One hundred sixty patients who had undergone hepatectomy for hepatoma were studied. In the operative findings of hepatoma, with a surgical margin of less than 10 mm, intrahepatic metastasis, tumor embolus in the second or more proximal branch of the portal vein, or lack of capsule formation related to the prognosis were the risk factors for recurrence. In 132 patients with these risk factors the survival rate of 19 patients with adjuvant arterial chemotherapy was significantly higher than for the 113 patients without it. Adjuvant hepatic arterial chemotherapy thus may be an effective therapy and should be studied prospectively in patients undergoing hepatectomy for high-risk hepatoma.**

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WITH THE INCREASED safety of hepatectomy due to recent advances in diagnostic procedures, including echography or computed tomography and postoperative management of liver surgery,[1,2] there has been a rapid increase in the number of hepatoma cases of hepatectomy, coupled with improved prognosis.[3,4] However it was reported that the intrahepatic recurrence rate after hepatectomy for hepatoma is high,[5,6] which makes it the key determinant for the surgical prognosis. Consequently some means to prevent intrahepatic recurrence is required to improve the prognosis after hepatectomy.

Therefore we administer adjuvant hepatic arterial chemotherapy after hepatectomy to prevent intrahepatic recurrence. In the present study, the relationship between operative findings of hepatoma and the postoperative prognosis was studied to clarify indications for adjuvant hepatic arterial chemotherapy after hepatectomy, and a high-risk group for recurrence was revealed. The results of adjuvant hepatic arterial chemotherapy performed in the high-risk group are presented.

## Materials and Methods

### *Hepatectomy*

Hepatectomy was undertaken in 193 patients with hepatoma at the Department of Surgery II, Nagoya University Hospital, Nagoya, Japan from January 1979 to May 1989. One hundred sixty of these patients, excluding 9 patients who had absolute noncurative resection, 17 patients who died during operation or hospital stay, and 7 patients who died from unrelated diseases, were studied. The patients consisted of 138 men and 22 women. Their ages ranged from 24 to 77 years, averaging 57.4 + 8.6 years. Liver cirrhosis was found in 128 patients (80%) with hepatomas. Forty-seven patients received lobectomy, 35 segmentectomy, 33 subsegmentectomy, and 45 partial hepatic resection. The final diagnosis of hepatoma and underlying hepatic disease was made histologically in all patients. The operative findings of the 160 patients were examined in relation to the recurrence and prognosis. Operative findings[7] included tumor size, capsule formation (Fc), intrahepatic metastasis (IM), tumor embolus in the portal vein (Vp), and surgical margin (TW). Cumulative percentage of survival and the disease-free survival rate were determined with the use of product-limited (Kaplan–Meier) estimate. The follow-up of all 160 patients was complete and the patient outcome was described as alive/dead or presence/absence of recurrence as of June 1, 1989. The confirmation of recurrence was made by

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echography, computed tomography, angiography, or pathologic findings (at re-resection or autopsy).

*Adjuvant Hepatic Arterial Chemotherapy*

Adjuvant hepatic arterial chemotherapy was performed in 23 patients who had undergone hepatectomy for hepatoma during these 2 years. These 23 patients included 2 patients with hepatectomy for recurrent hepatoma and 1 patient who died while hospitalized; 19 of the remaining 20 patients belonging to a high-risk group of recurrence were evaluated. In the adjuvant arterial chemotherapy cases, a heparin-coated catheter (PU Catheter, Toray, Japan) was inserted at hepatectomy through the gastroduodenal or the right gastroepiploic artery, and its tip was made to dwell in the hepatic artery (Fig. 1), with the other end connected to a reservoir (Catheter Access, Nipro, Japan) embedded in the subcutaneous layer of the abdominal wall. In such cases, the adjuvant arterial chemotherapy was started 2 to 6 weeks after operation. As for the drug administration, 250 mg/day of 5-fluorouracil (5-FU) was injected for 3 hours per day for 14 days from the reservoir, during which period 0.4 mg/kg of doxorubicin (Adriamycin; Adria Laboratories, Dublin, OH) and 0.12 mg/kg of mitomycin C suspended in an oily medium (lipiodol ultra fluid [Laboratoire Guerbet Co., Paris, France] using same dosage) were injected twice in single doses into the hepatic artery from the reservoir on days 1 and 8. The above was defined as one course, and the hepatic arterial chemotherapy was repeated every 3 months for 1 year.

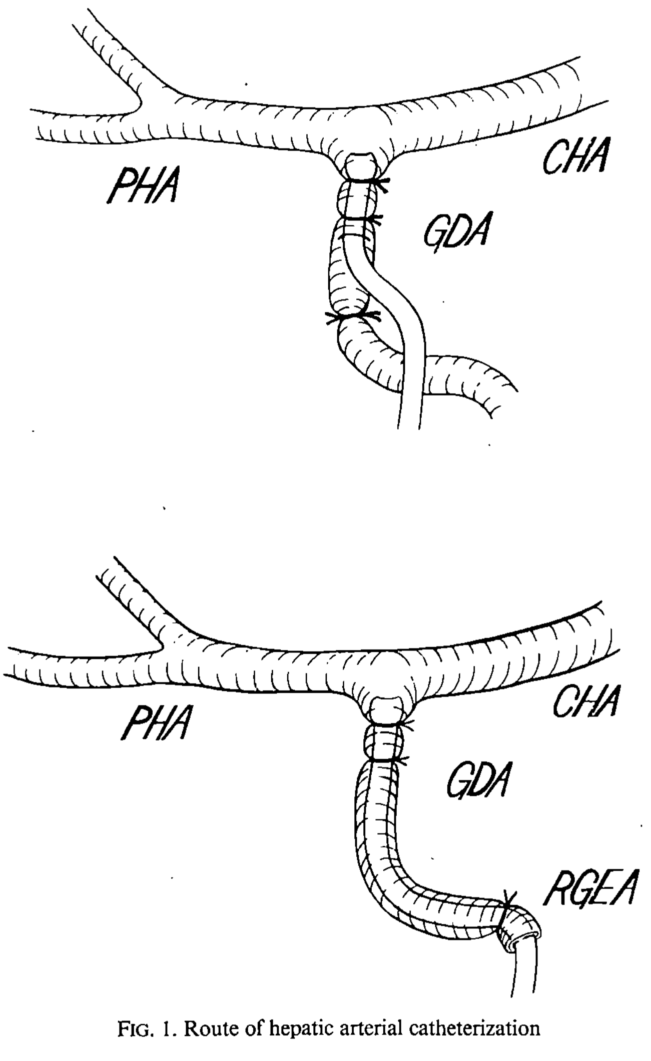


FIG. 1. Route of hepatic arterial catheterization

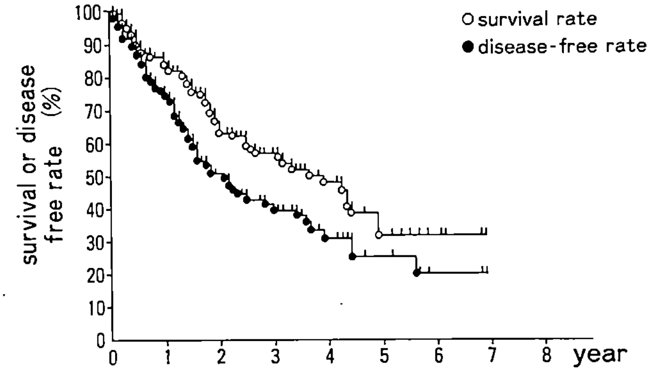


FIG. 2. Survival and disease-free rate after 160 hepatectomies for hepatoma.

## Results

*Risk Factors*

The 3- and 5-year survival rates for the 160 hepatoma patients were 55% and 32%, respectively. The 3- and 5-year disease-free survival rates were 40% and 25%, respectively. Therefore the 5-year recurrence rate was as high as 75% (Fig. 2). There were 73 patients who experienced recurrence and 71 patients (97%) had a recurrence in the remnant liver. The times from hepatectomy until recurrence were 1 year or less in 32 patients (43.7%), 1 to 2 years in 24 patients (32.9%), 2 to 3 years in 10 patients (13.7%), 3 to 4 years in 4 patients (5.5%), 4 to 5 years in 2 patients (2.7%), and 5 years or more years in 1 patient (1.4%). Time until recurrence in these patients was within 3 years (66 of 73 patients, 90.4%), but early recurrence within 1 year was found for most patients.

The operative findings of the hepatoma with respect to the prognosis were analyzed using the Kaplan–Meier estimate. The prognosis with surgical margin less than 10 mm (TW[+]), intrahepatic metastasis (IM[+]), tumor embolus in the second or more proximal branch of the portal vein (more than Vp 2), or lack of capsule formation (Fc[−]) indicated a significantly worse prognosis than the absence of these factors (Fig. 3). Thus these four criteria were considered high-risk factors for recurrence after hepatectomy for hepatoma. But in this series, tumor size did

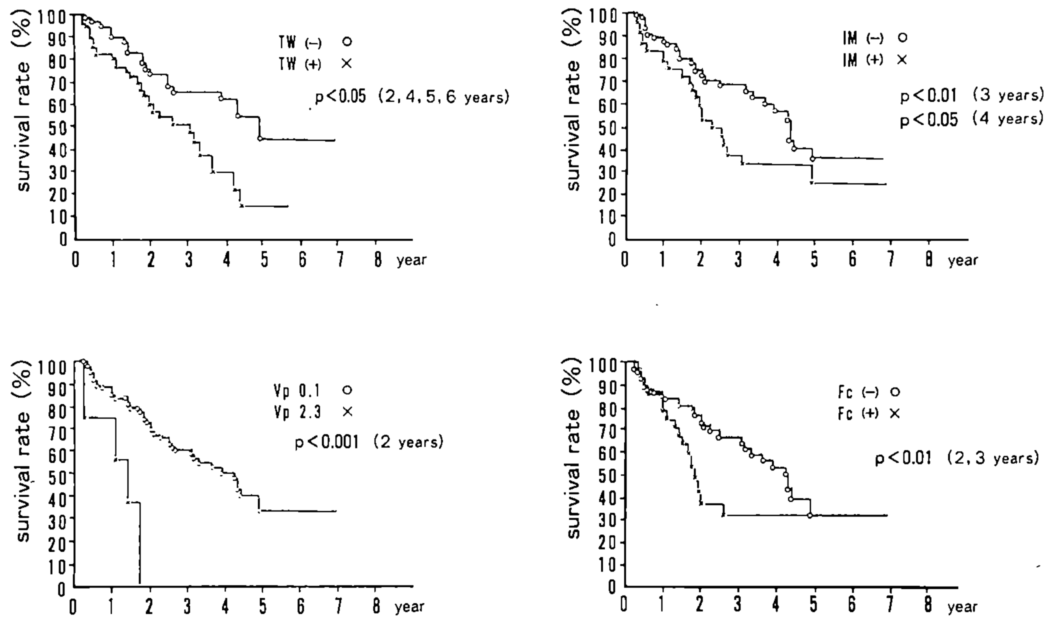


FIG. 3. Operative findings of hepatoma and survival rate after hepatectomy. TW(−) or TW(+): surgical margin more or less than 1 cm. Vp0, 1: no tumor invasion into the portal vein or invasion into the third or peripheral branch of portal vein. Vp2,3: tumor invasion into the second or more proximal branch of the portal vein. IM(−) or IM(+): with or without intrahepatic metastasis. Fc(−) or Fc(+): with or without fibrous capsule formation around the tumor.

not relate to the prognosis. Comparison of prognoses with and without these high-risk factors of recurrence showed that, while 3- and 5-year survival rates were 48% and 25% in patients with these risk factors, survival rates in patients with no risk factors were found to be 86% and 53%, respectively. A significant ($p < 0.001$, by generalized Wilcoxon test) difference was detected between the presence and absence of the risk factors (Fig. 4).

To improve the prognosis by decreasing the rate of recurrence in the remnant liver in patients with recurrence risk factors, adjuvant hepatic arterial chemotherapy was administered after hepatectomy. Among 160 hepatectomy patients, those with the recurrence risk factors amounted to 132. The survival rate of 19 patients receiving adjuvant arterial chemotherapy was compared with that of 113 patients not receiving it. The patients receiving adjuvant arterial chemotherapy all survived, except one who died of recurrence immediately after operation, indicating a significantly longer survival rate at 12 months than in the nontreated patients (Fig. 5). Recurrence was found in two patients who received adjuvant arterial chemotherapy. One was the patient who died immediately after operation, mentioned above, and the other was a patient who, while exhibiting the accumulation of lipiodol during the first course of hepatic arterial chemotherapy, suggesting recurrence, showed no growth of the tumor and is alive after 18 months because of the additional hepatic arterial chemotherapy.

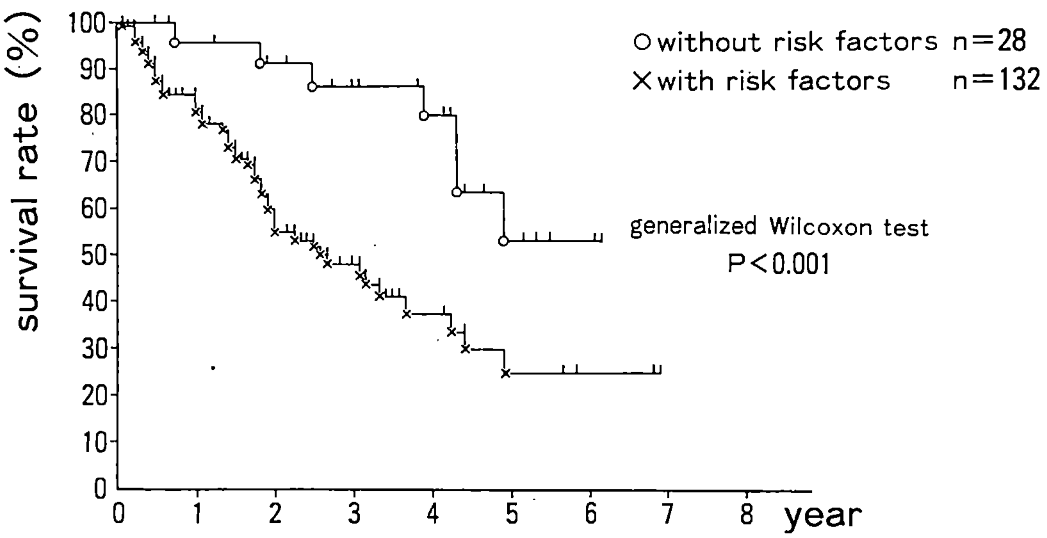


FIG. 4. Survival rate after hepatectomy for hepatoma with or without risk factor of recurrence. The group with the risk factor had at least one of four risk factors.

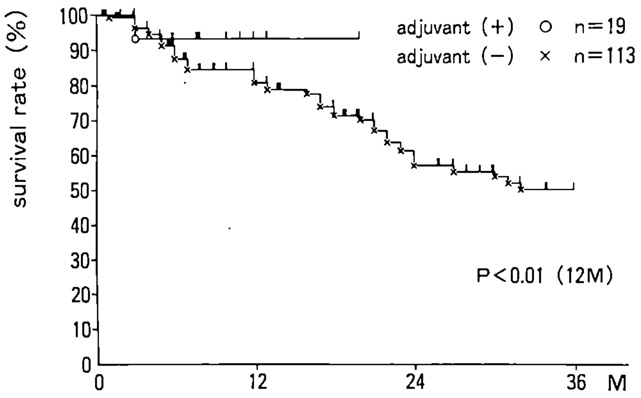


FIG. 5. Survival rate after hepatectomy with ot without adjuvant hepatic arterial chemotherapy in 132 hepatectomy patients with risk factor of recurrence.

## Complications

No serious complications attributable to the adjuvant arterial chemotherapy were observed. Some patients complained of transient fever or uncomfortable feelings after the injection of doxorubicin, mitomycin C, and lipiodol.

## Discussion

Most hepatoma recurrence takes place in the remnant liver early after operation.[5,6] Therefore we introduced adjuvant arterial chemotherapy to prevent recurrence after hepatectomy. Because hepatoma patients in Japan frequently experience concomitant liver cirrhosis, impaired liver function frequently is seen. To assure curability of hepatectomy for hepatoma, a sufficient distance is needed between the location of the tumor and the surgical margin. However because resected liver volume is restricted in the cases of poor liver function, sufficient distance is not always guaranteed. Our investigation revealed that patients with a surgical margin of less than 10 mm (TW[+]) had worse prognoses than those with TW(−). Among the operative findings, IM(+), Vp 2 or more, and Fc(−) were associated with the worsened prognoses, indicating that these are the high-risk factors. In addition, because cases with the recurrence risk factors belong to the high-risk recurrence group, adjuvant hepatic arterial chemotherapy was the recommended treatment.

It was reported that combined chemotherapy increased the partial response (PR) rate in unresectable primary liver cancer.[8,9] But when the drugs were administered systemically, the response rate was less than 20%. Hepatic arterial one-dose or infusion chemotherapy enhanced the sensitivity of hepatoma. Shibata et al.[10] reported PR in 46.5% of the patients by hepatic arterial one-dose injection of cisplatin suspended in an oily lymphographic agent. Sheen et al.[11] reported PR in 26% of hepatoma patients by hepatic arterial infusion of 5-FU together with bolus injection of mitomycin C and doxorubicin. Reed[12] showed effects of therapy in 70% of hepatoma patients by arterial infusion chemotherapy using 5-FU, 2-deoxyuridine. It was shown that etiodized oil (lipiodol) was retained only by the tumor tissue when it was administered in the hepatic artery. This led to application of hepatic arterial chemotherapy using an oily medium as a carrier of anti-cancer drugs for the treatment of hepatoma.[13] In our experience, doxorubicin and mitomycin C suspended in lipiodol administered concurrently with infusion of 5-FU as hepatic arterial chemotherapy have brought about partial responses in 18 of 32 (56.3%) unresectable hepatomas.[14] On the basis of this experience, we used infusion of 5-FU and one dose of doxorubicin, mitomycin C suspended in lipiodol in the adjuvant hepatic arterial chemotherapy after hepatectomy.

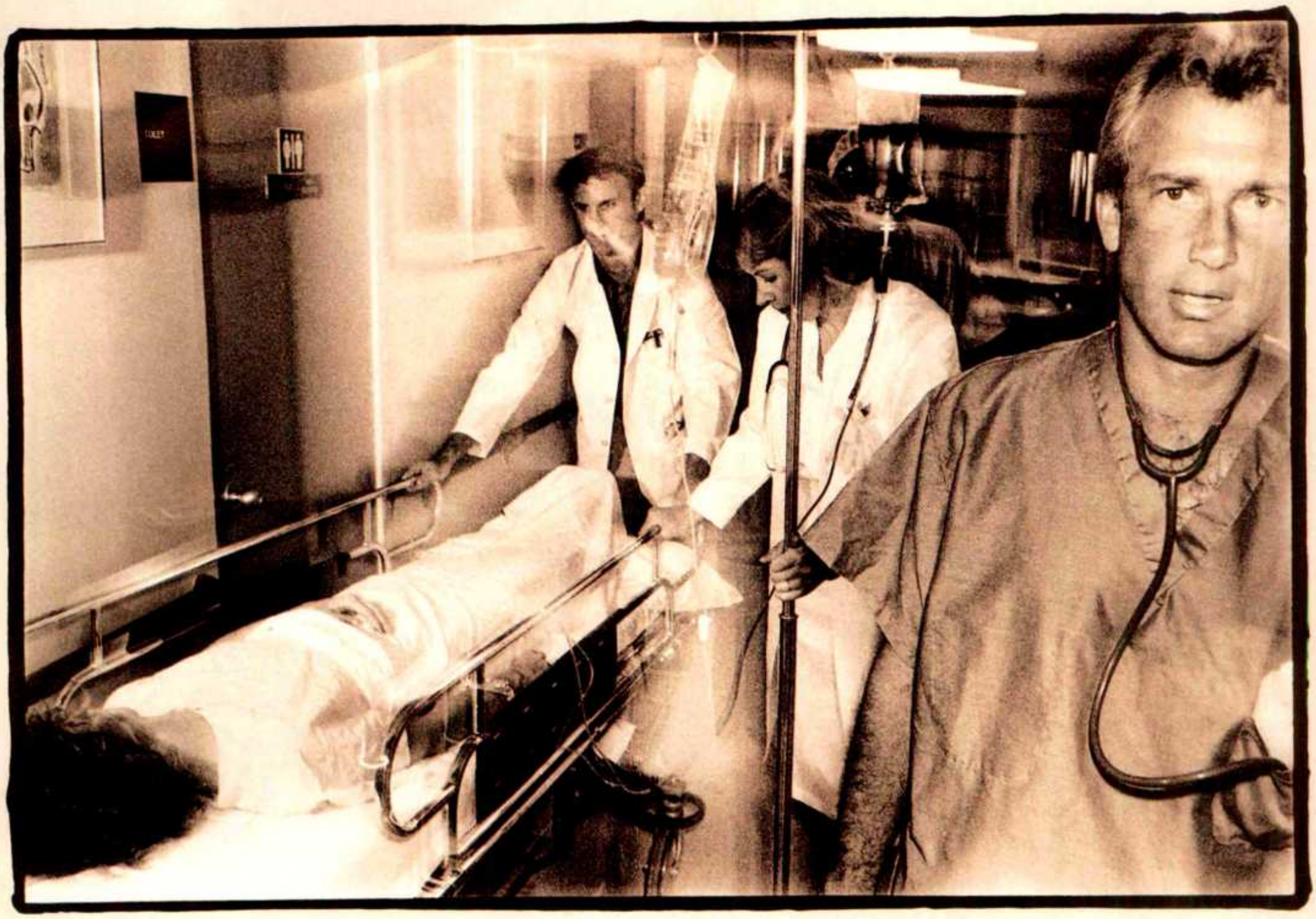
It is reported that oral administration of 5-FU as adjuvant therapy after hepatectomy did not prevent the recurrence of hepatoma.[15] While transarterial embolization before hepatectomy for hepatoma reportedly does not influence postoperative hepatoma recurrence,[16,17] there have been no reports on the use of hepatic arterial chemotherapy as adjuvant therapy after hepatectomy. In this context, we tried adjuvant arterial chemotherapy after hepatectomy to improve prognosis. Another useful aspect of adjuvant arterial chemotherapy was early detection of tumor recurrence as exhibited in the recurrence survival case.

While no serious complications attributable to the adjuvant arterial chemotherapy were observed, some patients complained of transient fever or discomfort after the injection of doxorubicin, mitomycin C, and lipiodol. If the drug flows into the gastrointestinal artery or back into the common hepatic artery, gastric or duodenal ulcer may result. To prevent these complications, hepatic arterial injection should be performed after sufficient recovery of liver functions after hepatectomy. A single-dose arterial injection should be conducted under fluoroscopic imaging monitor so the drug suspension does not flow into sites other than the hepatic artery. Sufficient attention must also paid to variations in liver function, platelets, and white blood cells.

From correlated examination of the operative findings of hepatoma and the prognosis, the high-risk factors of recurrence were found to consist of a surgical margin of less than 10 mm, positive intrahepatic metastasis, tumor invasion into the second branch or more proximal sites of portal vein, and the lack of fibrous capsule formed around the tumor. When patients with the risk of hepatoma recurrence were treated with adjuvant hepatic arterial chemotherapy, an improved survival rate was observed compared to patients with whom this therapy was not used. Consequently the present method may be an effective adjuvant therapy for patients undergoing hepatectomy for high-risk hepatomas, and prospective, randomized studies are needed to evaluate definitively this strategy.

## References

1. Ekberg H, Tranberg KG, Anderson R, et al. Major liver resection: perioperative course and management. Surgery 1986; 100:1-8.
2. Nonami T. Systemic hemodynamics and oxygen metabolism after hepatectomy: effect of hyperdynamic systemic circulatory support on postoperative prognosis. Journal of the Japanese Surgical Society 1985; 86:148-159.
3. Okamoto E, Tanaka N, Yamanaka N, et al. Results of surgical treatments of primary hepatocellular carcinoma: some aspects to improve long-term survival. World J Surg 1984; 8:360-366.
4. Sesto ME, Vogt DP, Hermann RE. Hepatic resection in 128 patients: a 24-year experience. Surgery 1987; 102:846-851.
5. Lin TY, Lee CS, Chen KM, et al. Role of surgery in the treatment of primary carcinoma of the liver: a 31-year experience. Br J Surg 1987; 74:839-842.
6. Nagao T, Goto S, Kawano N, et al. Hepatic resection for hepatocellular carcinoma clinical features and long-term prognosis. Ann Surg 1987; 205:33-40.
7. Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. Jap J Surg 1989; 19:98-129.
8. Falkson G, Coetzer BJ. Application and results of different chemotherapy regimens in primary liver Malignancies. *In* Herfarth C, Schlag P, Hohenberger P, eds. Therapeutic strategies in primary and metastatic liver cancer. Berlin, FRG: Springer-Verlag, 1986, p 103-111.
9. Chlebowski RT, Chan KK, Tong MJ, et al. Adriamycin and methyl-CCNU combination therapy in hepatocellular carcinoma. Cancer 1981; 48:1088-1095.
10. Shibata J, Fujiyama S, Sato T, et al. Hepatic arterial injection chemotherapy with cisplatin suspended in an oily lymphographic agent for hepatocellular carcinoma. Cancer 1989; 64:1586-1594.
11. Sheen MC, Huang TJ, Sheen PC, et al. Continuous intra-arterial infusion chemotherapy of hepatoma. J Formosan Med Assoc 1983; 82:389-398.
12. Reed ML, Vaitkevicius VK, Al-Sarraf M, et al. The practicality of chronic artery infusion therapy of primary and metstatic malignancies. Cancer 1981; 47:402-409.
13. Konno T, Maeda H, Iwai K, et al. Selective targeting of anti-cancer drug and simultaneous image inhancement in solid tumors by arterially administered lipid contrast medium. Cancer 1984; 54: 2367-2374.
14. Nonami T, Takagi H. The role of hepatic arterial infusion chemotherapy for hepatoma. Jap J Gastroenterol 1989; 86:1885.
15. Kanematsu T, Matsumata T, Takenaka K, et al. Clinical management of recurrent hepatocellular carcinoma after primary resection. Br J Surg 1988; 75:203-206.
16. Hwang TL, Chen MF, Lee TY, et al. Resection of hepatocellular carcinoma after transcatheter arterial embolization: reevaluation of the advantages and disadvantages of preoperative embolization. Arch Surg 1987; 122:756-759.
17. Takayasu K, Muramatsu Y, Moriyama N, et al. Clinico-radiological evaluation of recurrence in the residual liver following hepatectomy in 97 patients with hepatocellular carcinoma. Jap J Gastroenterol 1987; 84:1424-1432.



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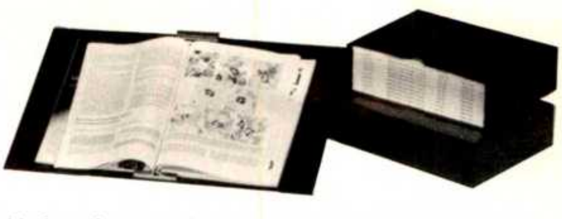

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# Unasyn® IM IV

(ampicillin sodium/sulbactam sodium)

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**References:**

**1.** Data available on request from Roerig. **2.** Aldridge KE, Sanders CV, Marier RL: Variation in the potentiation of β-lactam antibiotic activity by clavulanic acid and sulbactam against multiply antibiotic-resistant bacteria. *J Antimicrob Chemother* 1986;17:453-469. **3.** Crombleholme WR, Ohm-Smith M, Robbie MO, et al: Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. *Am J Obstet Gynecol* 1987;156(Feb):507-512. **4.** Cucharal G, Snydman D, Jacobus N, et al: Comparison of new antimicrobial agents against the *Bacteroides fragilis* group. Abstract, presented at the Annual Meeting of the American Society of Microbiology, Miami Beach, Fla, May 1988. **5.** D'Amato RF, Hochstein L, Pavia M: *In vitro* susceptibilities of aerobic and anaerobic clinical isolates to ampicillin/sulbactam. Presented as a Scientific Exhibit at the 87th Annual Meeting of the American Society of Microbiology, Atlanta, March 1987. **6.** Finegold SM: Anaerobic bacteria: Their role in infection and their management. *Postgrad Med* 1987;81(8):141-147. **7.** Jenkins SG: Susceptibility patterns of *Bacteroides fragilis* group isolates to ampicillin/sulbactam and other selected antibiotics. Presented at a symposium entitled *Ampicillin/Sulbactam: New Strategy for the Treatment of Infectious Disease*, Montreux, Switzerland, July 16-17, 1987, pp 19-20. **8.** Tally FP, Jacobus NV: Activity of sulbactam against recent isolates of aerobic and anaerobic bacteria, abstract 36. Presented at the 23rd International Congress of Antimicrobial Agents and Chemotherapy, Las Vegas, Oct 24-26, 1983 (abs). **9.** Wasilauskas B: Susceptibility of anaerobes to ampicillin-sulbactam and 6 other antimicrobial agents, abstract. Presented at the Annual Meeting of the American Society for Microbiology, Miami Beach, Fla, May 8-13, 1988. **10.** Wexler HM, Harris B, Carter WT, et al: In vitro efficacy of sulbactam combined with ampicillin against anaerobic bacteria. *Antimicrob Agents Chemother* 1985;27:876-878. **11.** Ampicillin/sulbactam (Unasyn). *Med Lett Drugs Ther* 1987;29(August 28):79-81. **12.** Hemsell DL, Wendel GD, Hemsell PG: Combating beta-lactamase enzyme—principal defense mechanism of many pelvic infection pathogens. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **13.** Senft H-H, Stiglmayer R, Eibach HW, et al: Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. *Drugs* 1986;31(suppl 2):18-21. **14.** Newton ER, Gibbs RS: Treatment of postpartum endometritis: A comparison of ampicillin/sulbactam vs. gentamicin plus clindamycin. Presented as a scientific exhibit at the Thirty-Sixth Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, Boston, May 2-4, 1988. **15.** Gunning J: A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. *Drugs* 1986;31(suppl 2):14-17. **16.** Stromberg BV, Reines HD, Hunt P: Comparative clinical study of sulbactam and ampicillin and clindamycin and tobramycin in infections of soft tissues. *Surg Gyn Obstet* 1986;162:575-578. **17.** Kager L, Malmborg AS, Nord CE, et al: A randomized controlled trial of ampicillin plus sulbactam vs. gentamicin plus clindamycin in the treatment of intraabdominal infections: A preliminary report. *Rev Infect Dis* 1986;8(suppl 5):S583-S588. **18.** Bruhat MA, Pouly JL, Le Boedec G, et al: Treatment of acute salpingitis with sulbactam/ampicillin: Comparison with cefoxitin. *Drugs* 1986;31(suppl 2):7-10. **19.** Faro S: Experience with ampicillin/sulbactam for OB/GYN infections. Presented at a symposium entitled *β-Lactamase Inhibitors: Progress with Ampicillin/Sulbactam*, Atlanta, December 6, 1987, p 14 (abs).

**INDICATIONS AND USAGE**

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

**Skin and Skin Structure Infections** caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

**Intra-Abdominal Infections** caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

**Gynecological Infections** caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

**CONTRAINDICATIONS**

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

**WARNINGS**

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

**PRECAUTIONS**

**General:** A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

**Drug Interactions:** Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

**Drug/Laboratory Test Interactions:** Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

**Pregnancy**

**Pregnancy Category B:** Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

**Labor and Delivery:** Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

**Nursing Mothers:** Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

**Pediatric Use:** The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

**ADVERSE REACTIONS**

UNASYN is generally well tolerated. The following adverse reactions have been reported.

**Local Adverse Reactions**

Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%

**Systemic Adverse Reactions**

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

**Adverse Laboratory Changes**

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

*Hepatic:* Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
*Hematologic:* Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
*Blood Chemistry:* Decreased serum albumin and total proteins.
*Renal:* Increased BUN and creatinine.
*Urinalysis:* Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

**Gastrointestinal:** Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

**Hypersensitivity Reactions:** Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

**Hematologic:** In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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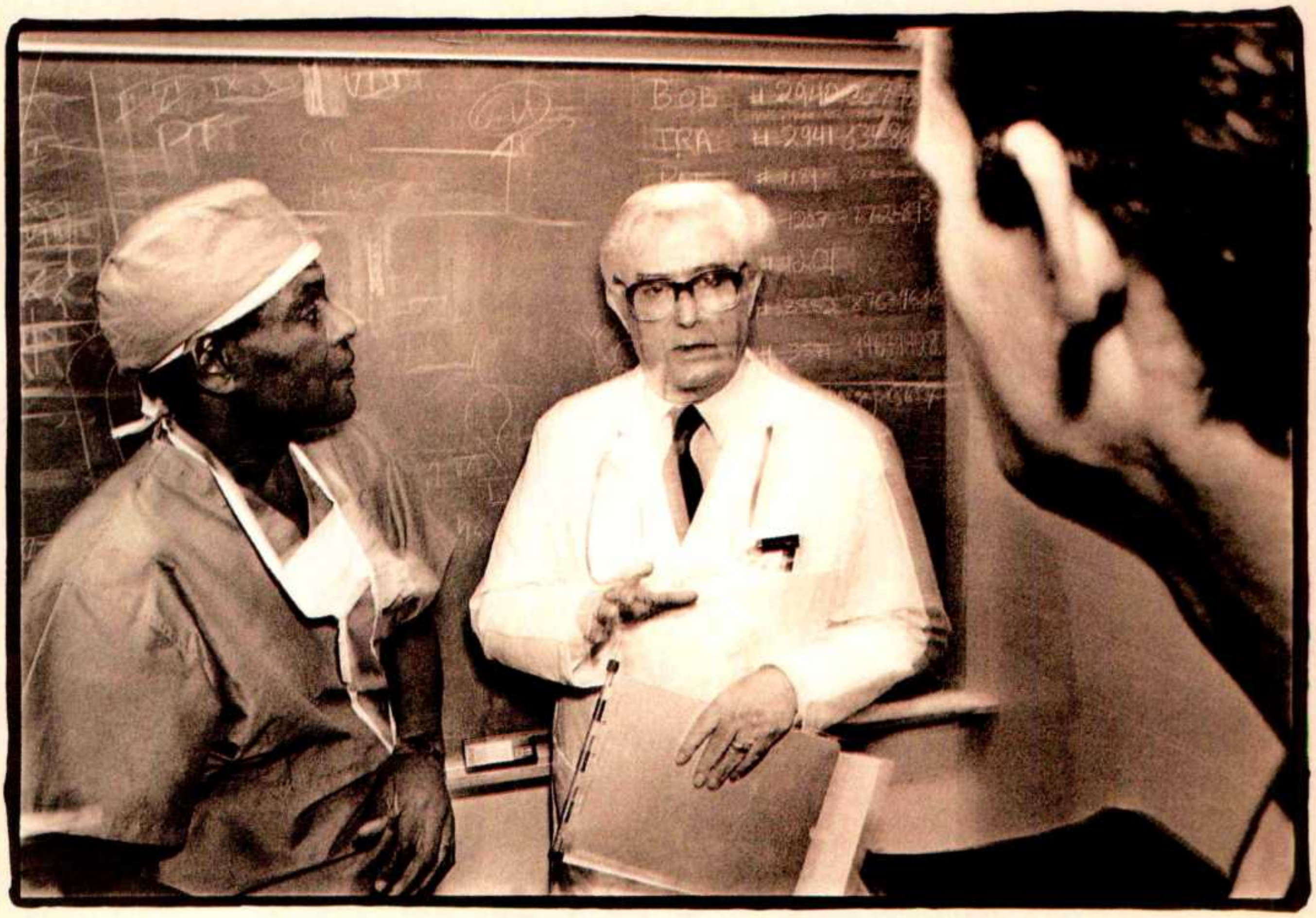

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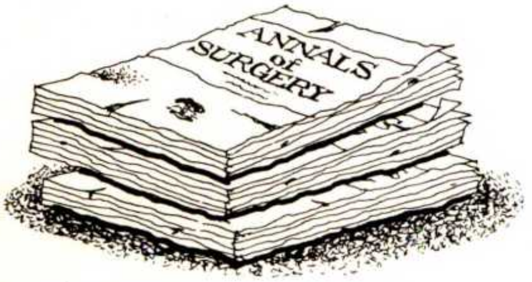

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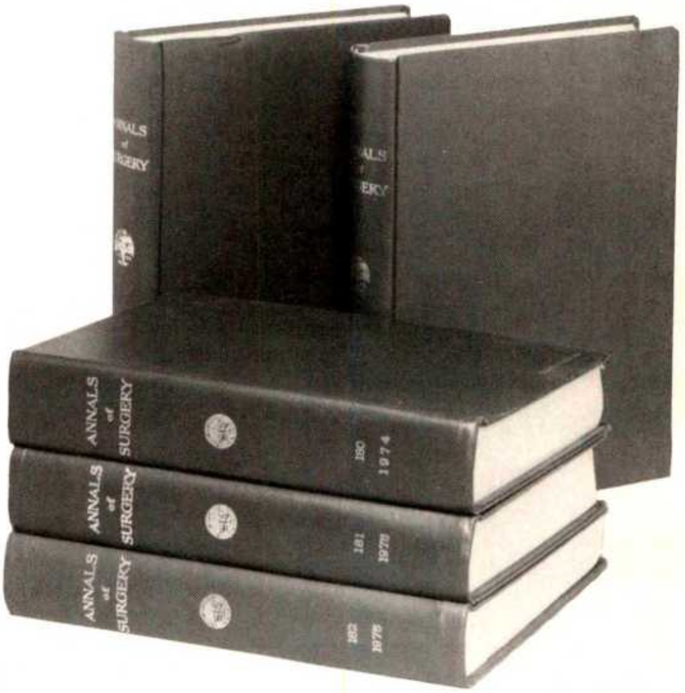

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# Human Liver Regeneration After Major Hepatectomy

## *A Study of Liver Volume by Computed Tomography*

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**Regeneration of the remnant liver after major hepatectomy in humans was studied by computed axial tomography (CT) in 12 noncirrhotic and five cirrhotic patients. Liver volumes were measured by abdominal CT 3 days, 10 days, 3 months, 6 months, 1 year, and 1.5 years after resection. Of the 17 patients, liver remnant volume was increased in 21.2% ± 6.7% and 30.6% ± 12.7% at 3 months and 6 months after resection, respectively. Noncirrhotic livers were 28.4% ± 9.5% and 48.4% ± 17.8% larger at 3 and 6 months. For cirrhotic livers, the increase was 8.5% ± 3.6% and 12.9% ± 4.5%. In five patients with right hepatectomy (65% resection), the liver remnant volumes were increased 38.4% ± 11.7%, 48.0% ± 16.2% and 95.1% ± 4.5% at 3 months, 6 months, and 1 year after resection, respectively. In seven patients with right partial hepatectomy (30% to 35% resection), the percentages were 7.4% ± 3.2%, 21.8% ± 8.4%, and 63.9% ± 18.3% and in five patients with left lateral segmentectomy (15% resection), they were 15.6% ± 8.2%, 27.8% ± 12.2%, and 33.0% ± 14.5% 3 months, 6 months, and 1 year after resections, respectively. Noncirrhotic livers showed better regeneration than cirrhotic livers. Complete regeneration took about 1 year. The noncirrhotic liver that underwent right lobectomy also needed 1 year to double its postresection volume.**

ANIMAL EXPERIMENTATION HAS shown the remarkable regenerative and restorative power of the liver after hepatic resection.[1-4] In humans functional and metabolic restoration can be found within 2 to 3 weeks after major hepatectomy.[5,6] The normal liver remnant regeneration has been proved at secondary laparotomy[7] and restoration of normal liver mass has occurred within 6 months, as demonstrated by repeated liver scanning with rose bengal $I^{131}$ or $Tc^{99}$.[8,9] Therefore information on the rate of liver regeneration in humans is incomplete. There has been no satisfactory method for accurate and repeated measurement of liver volume and size. And whether the cirrhotic liver remnant can be regenerated is still controversial.[8]

The recent advent of computed tomography (CT) has made possible a noninvasive, *in situ* measurement of the volume of various organs in the body.[10] Attempts to use the CT method to measure the liver volume and mass when studying liver regeneration in cirrhotic and noncirrhotic patients were inevitable.

### Patients and Methods

Seventeen patients who underwent major hepatic resection due to liver trauma (3 patients), hepatolithiasis (4 patients), and hepatocellular carcinoma (HCC) (10 patients) at the Department of Surgery, Chang Gung Memorial Hospital, Taipei, Taiwan, during the 2-year period from 1987 through 1988[11] were included in the study. There were 12 men and 5 women. Their ages ranged from 24 to 72 years. Among them five patients with HCC were found to have associated liver cirrhosis. They were in the compensatory stage without evidence of ascites or jaundice.

Of the 17 patients, right lobectomy (hemihepatectomy) was done in 5, right partial hepatectomy (bisegmentectomy) in 7, and left lateral segmentectomy in 5 (Table 1).

Abdominal CT scan was performed 3 days, 10 days, 3 months, 6 months, 1 year, and 1.5 years after hepatectomy. Computed tomography scans transversing the whole liver were made with a cycle time of 5 seconds at intervals of 1 cm. To demonstrate the section margin more clearly, enhancement by an intravenous bolus injection of contrast medium was used routinely. The right and left lobes of the liver were separated by a line passing through the gallbladder and inferior vena cava (Cantlie

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TABLE 1. *Seventeen Patients Underwent Major Hepatectomy*

| Pattern of Hepatectomy | HCC | Trauma | Hepatolithiasis | Total |
|---|---|---|---|---|
| Right lobectomy | 4 | 1 | 0 | 5 |
| Right partial lobectomy (bisegmentectomy) | 5* | 2 | 0 | 7 |
| Left lat segmentectomy (left partial lobectomy) | 1 | 0 | 4 | 5 |
| Total | 10 | 3 | 4 | |

* Liver cirrhosis.

TABLE 2. *Increased Percentage of Liver Volume in Cirrhotic or Noncirrhotic Patients*

| With or Without Liver Cirrhosis | 3 months | 6 months |
|---|---|---|
| All patiens (n = 17) | 21.2 ± 6.7% | 30.6 ± 12.7% |
| Noncirrhosis (n = 12) | 28.4 ± 9.5% | 48.4 ± 17.8% |
| Cirrhosis (n = 5) | 8.5 ± 3.6% | 12.9 ± 4.5%* |

* $p < 0.05$, compared to the noncirrhotic group.

line) in a cut to permit visualization of both markers. A division between the left lateral and medial segments was drawn through the left sagittal fissure. The areas of the entire liver, lobe, or segment were measured, respectively, by planimetry. The volume of each part then was calculated by multiplication of the area of each part by interval thickness and magnification index and addition of the interval volume of each part.[10]

## Results

Of the 17 patients, the liver remnant volume was increased 21.1% ± 6.7% and 30.6% ± 12.7% 3 and 6 months after resection, respectively. Noncirrhotic livers in 12 patients were 28.4% ± 9.5% and 48.4% ± 17.8% increased in comparison with 8.5% ± 3.6% and 12.9 ± 4.5% for cirrhotic livers in five patients 3 and 6 months after resection, respectively (Table 2).

Postoperative progressive increase in liver remnant volume was found in various types of hepatectomy. In five patients with right lobectomy, the liver remnant volume was increased 38.4% ± 11.7%, 48.0% ± 16.2%, and 95.1% ± 24.5% after resection 3 months, 6 months, and 1 year, respectively. In seven patients with right bisegmentectomy, the percentage of increase was 7.4% ± 3.2%, 21.8% ± 8.4%, and 63.9% ± 18.3%, respectively, at 3 months, 6 months, and 1 year. In five patients with left lateral segmentectomy, the percentages of increase were 15.6% ± 8.2%, 27.8% ± 12.2%, and 33.0% ± 14.5% larger (Tables 3 and 4). It seemed that the greater the volume of liver resected, the greater the restoration capacity.

TABLE 4. *Increased Percentage of Liver Volume After Hepatectomy*

| Pattern of Hepatectomy | 3 months (%) | 6 months (%) | 1 year (%) |
|---|---|---|---|
| S/P right lobectomy (n = 5) | 38.4 ± 11.7 | 48.0 ± 16.2 | 95.1 ± 24.5 |
| S/P right partial lobectomy (n = 7) | 7.4 ± 3.2 | 21.8 ± 8.4 | 63.9 ± 18.3 |
| S/P left partial lobectomy (n = 5) | 15.6 ± 8.2 | 27.8 ± 12.2 | 33.0 ± 14.5 |

## Discussion

Computed axial tomography permits accurate cross-sectional radiographic visualization of visceral organs. In clinical use of CT, some organ movement and incomplete resolution from the surrounding structure cannot be avoided. In many studies the preoperative CT estimation of volume of liver was compared with the actual measured volume of the resected specimen. The results indicated a close linear relationship between the CT volumes and the actual volumes, and the average difference was within ±3% to 5%.[10] The difference suggests that this method, the quantitative CT technique, is sufficiently accurate for clinical use.

Extensive research has been directed at identifying the factors responsible for initiation and regulation of liver regeneration.[12–14] Recently it was demonstrated that portal blood is important for restoration of the liver.[14] When a hepatic lobe is removed, portal flow to the liver remnant is increased immediately. In the noncirrhotic liver, the bulk of the remaining liver remnant can increase rapidly due to vascular engorgement and interstitial edema. However the new circumstance created by hepatic lobectomy cannot be adjusted for immediately by a cirrhotic liver remnant.[14]

In our study we found that remnants of noncirrhotic liver can increase gradually in size by about 30%, increasing in 3-to-4–month intervals. Usually it took about 1

TABLE 3. *Changes of Liver Volume After Hepatectomy or After Different Operation*

| Pattern of Hepatectomy | Postop. (cm$^3$) | 3 months (cm$^3$) | 6 months (cm$^3$) | 1 year (cm$^3$) |
|---|---|---|---|---|
| S/P right lobectomy (n = 5) | 541.8 ± 81.5 | 715.9 ± 81.2 | 801.8 ± 10.2 | 1056.8 ± 40.5 |
| S/P right partial lobectomy (n = 7) | 985.9 ± 110.2 | 1023.4 ± 120.2 | 1201.2 ± 80.4 | 1302.6 ± 20.4 |
| S/P left partial lobectomy (n = 5) | 1038.4 ± 3.9 | 1273.7 ± 28.6 | 1360.1 ± 20.8 | 1380.8 ± 15.6 |

year to double a postresection volume after right lobectomy. As for regeneration of cirrhotic livers, although Lin et al.[8] reported that they failed to see any change in size of remnant on repeated liver scans, we found that they do have restoration capacity. Of course cirrhotic livers are less able to regenerate than noncirrhotic livers.

The proportion of each segment in the human liver has been estimated as 35% for the right posterior (segments VII and VIII), 30% for the right anterior (segments VI and V), 20% for the left medial (segment IV), and 15% for the left lateral segment (segments II and III).[15] Surgeons assess the extent of hepatectomy conventionally by adding the percentages of the resected segments. For example 65% is allocated to right lobectomy and 35% to left lobectomy. In our series, we found remarkable regeneration of the liver remnant in those who underwent right lobectomy (60% resection) in comparison with other types of hepatectomy, such as right partial (30% to 35% resection) and left lateral segmentectomy (15%).

During operation resection progressively removes increasing numbers of vascular outflow tracts. With resections of less than 30%, significant obstruction and the resulting vascular pooling is rare. However hepatectomies excising greater amounts of liver lead to an increase in total hepatic blood flow and vascular engorgement. This is probably the reason why striking regeneration occurred in the remaining left liver after right hepatic lobectomy. Unlike opinions expressed in other reports, we do not think there is any time difference for complete liver regeneration between the patients with noncirrhotic HCC and those with other benign disease who underwent hepatectomy. Lin et al.[8] reported that the remaining left liver regenerated within 3 months after right lobectomy in liver cyst patients. In HCC patients Lin et al.[8] concluded that it took about 6 months to complete the regeneration process. But in both Lin's report and ours, the number of patients in the study is too small to support any definite conclusion.

## References

1. Bucher NLR. Experimental aspects of hepatic regeneration. N Eng J Med 1967; 277:686–696.
2. Lee S, Edgington TS, Orloff MJ. The role of afferent blood supply in regeneration of liver isografts in rats. Surg Forum 1968; 19: 360.
3. Lee S, Broelsch CE, Flamant YM, et al. Liver regeneration after portacaval transposition in rats. Surgery 1975; 77:144–149.
4. Moolter FL, Bucher NLR. Regeneration of rat liver. Transfer of humoral agent by cross circulation. Science 1967; 158:272–274.
5. McDermott WV Jr, Greenberger NJ, Isselbacher KJ, Weber AL. Major hepatic resection: diagnostic techniques and metabolic problems. Surgery 1963; 54:56–66.
6. Pack GT, Islami AH, Hubbard JC, Brasfield RD. Regeneration of human liver after major hepatectomy. Surgery 1962; 52:617–623.
7. Aronsen KF, Bengmark S, Dahlgren S, et al. Liver resection in the treatment of blunt injuries to the liver. Surgery 1968; 63:236–246.
8. Lin TY, Lee CS, Chen CC, Liaw KY, Lin WSJ. Regeneration of human liver after hepatic lobectomy studied by repeated liver scanning and repeated biopsy. Ann Surg 1979; 190:48–53.
9. Starzl TE, Pntnum CW, Groth CG, et al. Alopecia, ascites and incomplete regeneration after 85 to 95 percent liver resection. Am J Surg 1975; 129:587–590.
10. Heymsfield SB, Fulenwider T, Nordlinger B, et al. Accurate measurement of liver, kidney and spleen volume and mass by computerized axial tomography. Ann Inter Med 1979; 90:185–187.
11. Chen MF, Hwang TL, Jeng LB, et al. Hepatic resection in 120 patients with hepatocellular carcinoma. Arch Surg 1989; 124:1025–1028.
12. Fisher B, Szuch P, Fisher ER. Evaluation of a humoral factor in liver regeneration utilizing liver transplants. Cancer Res 1971; 31:322–331.
13. Lee S, Keiter JE, Rosen H, et al. Influence of blood supply on regeneration of liver transplants. Surg Forum 1969; 20:369.
14. Sgro JC, Charters AC, Chandler JG, et al. Studies of the site of origin of the hepatotrophic portal blood factor involved in liver regeneration. Surg Forum 1973; 24:377.
15. Stone HH, Long WD, Smith RB, Heynes CD. Physiologic considerations in major hepatic resections. Am J Surg 1969; 117:78–84.

# A Valved Hepatic Portoduodenal Intestinal Conduit for Biliary Atresia

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**Forty-six consecutive patients with biliary atresia were operated on at our institution during the 11-year period between 1978 and 1989. Their ages at operation ranged from 18 to 153 days (mean, 59 days). After dissecting the porta hepatis structures by Kasai operation, a biliointestinal anastomosis was constructed with a valved hepatic portoduodenal intestinal conduit in all cases. The intestinal valve is an intussuscepted muscular valve. Valvular function was examined radiologically. The upper gastrointestinal series demonstrated no reflux of contrast material into the conduit proximal to the valve and liver scintigraphy demonstrated that radioactive isotope drained readily into the duodenum through the valve. Thirty-nine of the forty-six patients (85%) had bile drainage after initial operation. At present 30 patients (65%) are alive without jaundice, 6 (13%) are alive with jaundice, and 10 (22%) are dead. The 5-year jaundice-free survival rate was 64%. Cholangitis occurred in 9 of 39 patients (23%) who had obtained apparent bile drainage: 5 had tractable cholangitis and 4 had refractory cholangitis. Reoperation restored bile flow in 2 of 8 patients who abruptly ceased to have bile drainage without cholangitis. In conclusion, with a valved hepatic portoduodenal intestinal conduit, the incidence of cholangitis was decreased, its medical control became easier, and the survival rate was improved.**

HEPATIC PORTOENTEROSTOMY FOR biliary atresia permits bile drainage[1] and immediate postoperative bile drainage is achieved in more than 80% of patients.[2,3] After obtaining bile drainage, ascending cholangitis is the most serious complication, leading to biliary reobstruction and/or progressive liver fibrosis.

Many types of biliointestinal reconstruction have been performed to prevent ascending cholangitis. In most procedures the incidence of postoperative cholangitis is more than 48%.[2,4] Hepatic portocholecystostomy is the only procedure producing excellent results with regard to postoperative cholangitis.[2,5] This procedure uses the valve mechanism of Vater's ampulla to prevent reflux of duodenal contents into the porta hepatis. However the indication for this method is limited by the types of complication and the anatomic circumstances.

At our institution a newly developed intestinal valve, an intussuscepted muscular valve, has been used as an isolated jejunal conduit for biliary atresia.[6] Its valvular function has been examined clinically and experimentally. In this communication we describe the key surgical features of the procedure and outline our long-term results.

## Materials and Methods

Forty-six consecutive patients with biliary atresia were operated on between May 1978 and August 1989 at our institution. Of the 46 patients, 28 were female and 18 were male. Their ages at operation ranged from 18 days to 153 days (mean, 59 days). Seven of the forty-six patients were younger than 30 days, 18 were between 31 and 60 days old, and 21 were more than 61 days old. Forty-three cases were type III and three were type I, according to the classification of the Japanese Society of Pediatric Surgeons.[7] The follow-up period ranged from 5 months to 11 years.

The diagnosis of postoperative cholangitis was made from the tetrad of unexplained fever (temperature > 38 C), elevated serum bilirubin level, acholic stools, and leukocytosis. Cholangitis was graded according to the severity of inflammation: (+) tractable cholangitis controlled by antibiotic therapy in an ambulatory setting; and (++) refractory cholangitis treated with hospitalization.

To evaluate the effectiveness of the valvular function in preventing the reflux of intestinal contents, upper gas-

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trointestinal (UGI) series were performed in 15 patients with biliary atresia more than 1 year after the operation. As a control UGI series were performed in 10 patients with choledochal cyst more than 1 year after hepaticojejunoduodenostomy without valve. On the other hand, the anterograde bile passage through the valve was examined with hepatobiliary scintigraphy in nine patients with biliary atresia more than 10 years after the operation.

Bacteriologic study was performed in eight patients who had sufficient bile drainage to examine bile after initial operation. Bile for culture was obtained by a sterile catheter inserted into the conduit proximal to the valve during operation. Culture results were expressed as logarithmic colony counts per milliliter.

### Operative Technique

After dissecting the porta hepatis structures by the Kasai operation, a biliointestinal anastomosis was constructed with a valved hepatic portoduodenal intestinal conduit in all patients (Fig. 1). An intestinal conduit measuring about 15 cm long was made from the jejunum. The proximal end of the segment was closed and the side of the segment was anastomosed to the porta hepatis. The distal end was anastomosed to the descending portion of the duodenum. A valve was established at the distal third of the conduit. An 8 French polyethylene catheter was inserted into the conduit proximal to the valve to decrease the pressure in the conduit and examine the bile flow for 1 week. A muscular valve was constructed in the following manner (Fig. 2). The vasa recti of the conduit were ligated and divided by the width equal to the intestinal diameter. The seromuscular layer of the devascularized intestine then was removed. The denuded segment and an equivalent length of its proximal portion of the intestine was intussuscepted into the distal segment. The intussuscepted valve was fixed with 8 to 10 interrupted sutures.

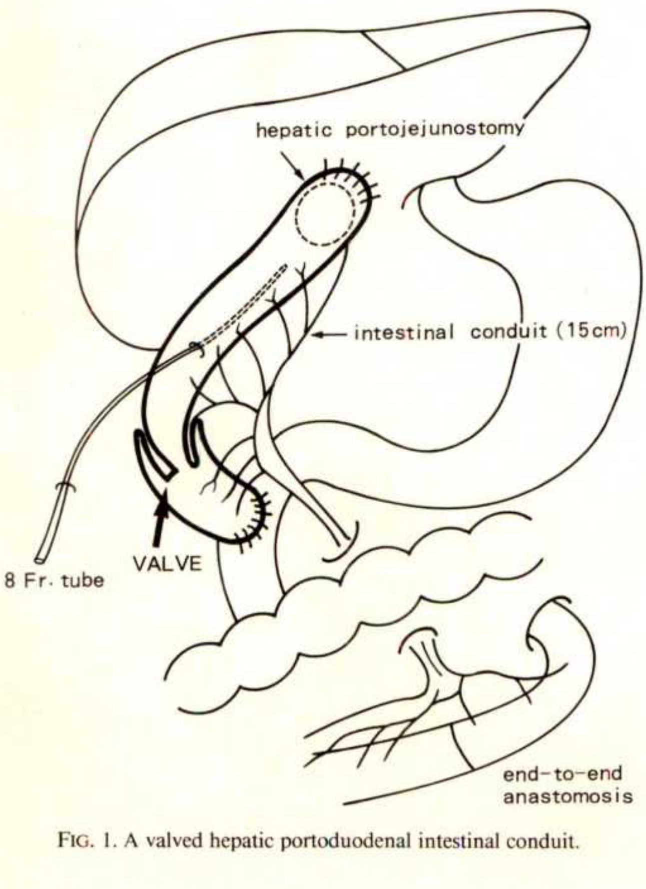

FIG. 1. A valved hepatic portoduodenal intestinal conduit.

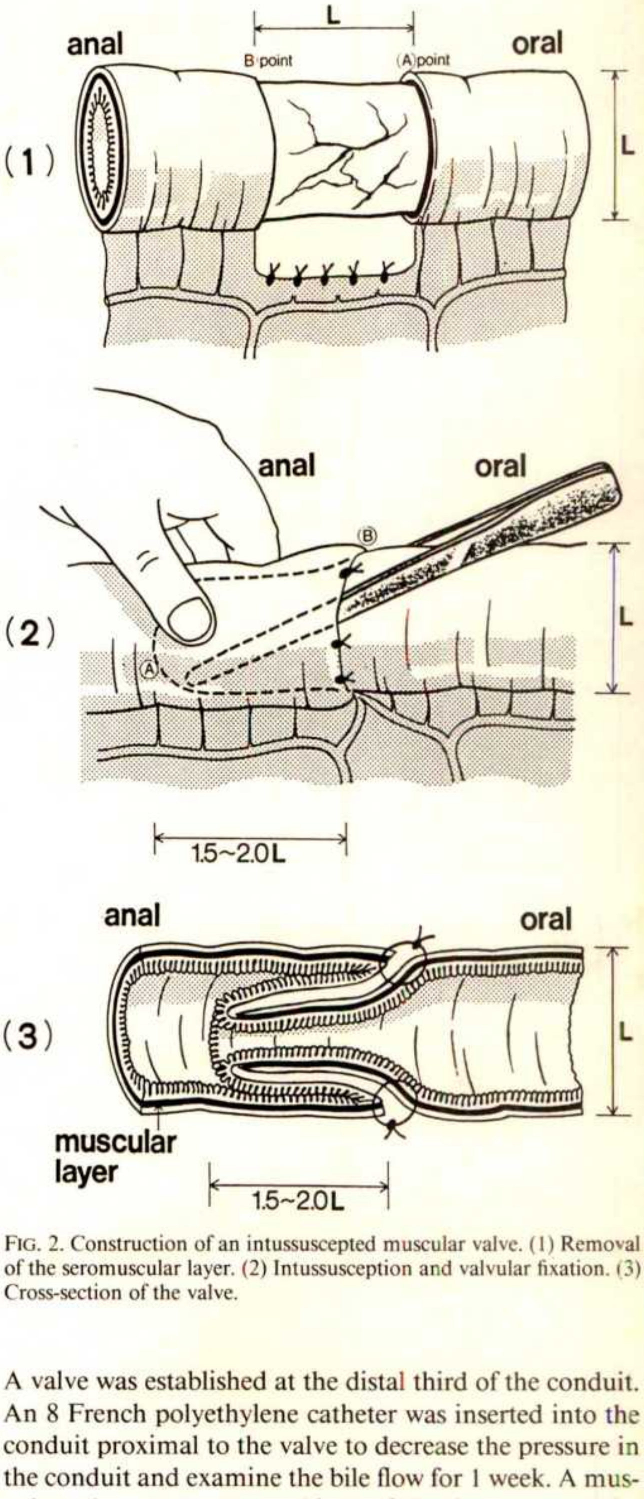

FIG. 2. Construction of an intussuscepted muscular valve. (1) Removal of the seromuscular layer. (2) Intussusception and valvular fixation. (3) Cross-section of the valve.

### Pre- and Postoperative Management

Kanamycin syrup was given orally for 2 or 3 days before the operation. As antibiotics, cephalosporin or penicillin for 4 weeks and aminoglycoside for 1 week were administered intravenously after the operation. Ursodesoxycholic acid, glucagon, and adrenocorticosteroid (prednisolone) were administered as choleretic agents for several weeks. Multivitamin compound and vitamin D (Alfarol®, Chugai Pharmaceutical Co., LTD., Tokyo, Japan) were given routinely.

## Results

### *Postoperative Bile Drainage*

Thirty-nine of the forty-six patients (85%) had bile drainage after initial operation (Fig. 3). Seven patients (15%) had no bile flow, one of which obtained bile drainage after reoperation. At present 30 patients (65%) are alive without jaundice, 6 patients (13%) are alive with jaundice, and 10 patients are (22%) dead. Sixteen of the twenty-five patients who were operated on before 1985 are alive without jaundice. The 5-year survival rate with the absence of jaundice is 64%.

### *Cholangitis*

Cholangitis occurred in 9 of 39 patients (23%) who had obtained apparent bile drainage: 5 patients had tractable cholangitis (+) and 4 patients had refractory cholangitis (++) (Fig. 4). All of the tractable patients are alive without jaundice and have almost normal liver function. Three of the refractory patients are alive without jaundice but have mild liver dysfunction. The other patient has liver cirrhosis with jaundice and is awaiting liver transplantation.

### *Reoperation*

Eight of the thirty-nine patients (21%) abruptly ceased to have bile drainage without cholangitis. All patients underwent reoperation for scoring of the liver hilus and revision of the hilar anastomosis. Laparotomy revealed that the porta hepatis was covered with thick granulation in all cases. Two of the eight patients became jaundice free again and have regained almost normal liver function. Two patients have liver cirrhosis with jaundice and are awaiting liver transplantation. The remaining patients died of liver failure, pneumonia, disseminated intravascular coagulation, and complication after liver transplantation.

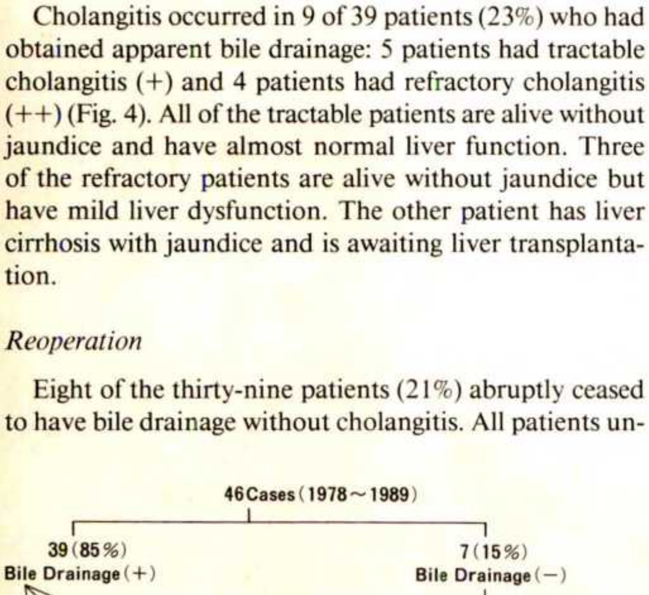

FIG. 3. Overall results after surgery.

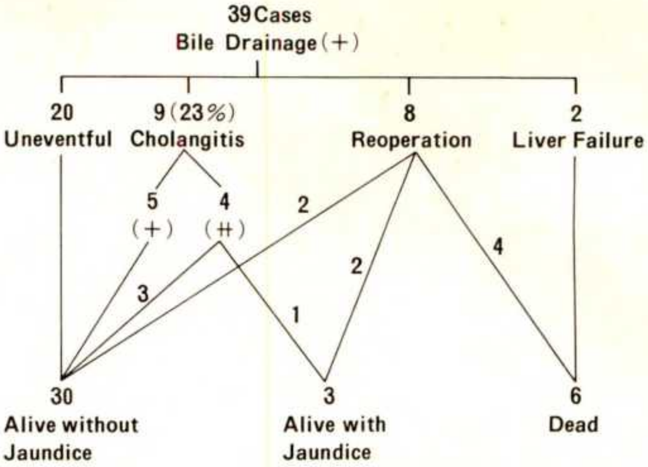

FIG. 4. Results after obtaining bile drainage.

Seven of the forty-six patients (15%) had no bile flow after initial operation and underwent reoperation (Fig. 3). One of these patients obtained bile drainage and is alive with jaundice.

### *Valvular Competence*

In 15 patients with biliary atresia, UGI series demonstrated no reflux of contrast material into the conduit proximal to the intussuscepted muscular valve (0 of 15, 0%) (Fig. 5A). In contrast 5 of 10 patients with choledochal cyst had reflux of contrast material into the intrahepatic bile duct (5 of 10, 50%) (Fig. 5B). Hepatobiliary scintigraphy demonstrated that radioactive isotope drained readily into the duodenum through the valve in all nine cases examined (Fig. 6).

Both qualitative and quantitative cultures of bile drainage confirmed enteric bacteria in six of eight cases (Table 1). Colonization of the intestinal conduit began within the first few weeks after the operation.

## Discussion

The pathogenesis of cholangitis after Kasai operation is conjectured to be due to pre-existing cholestasis and bacterial contamination.[3,8,9] That is, because the intrahepatic bile ducts are to some extent hypoplastic and stenotic in all patients with biliary atresia, cholestasis arises

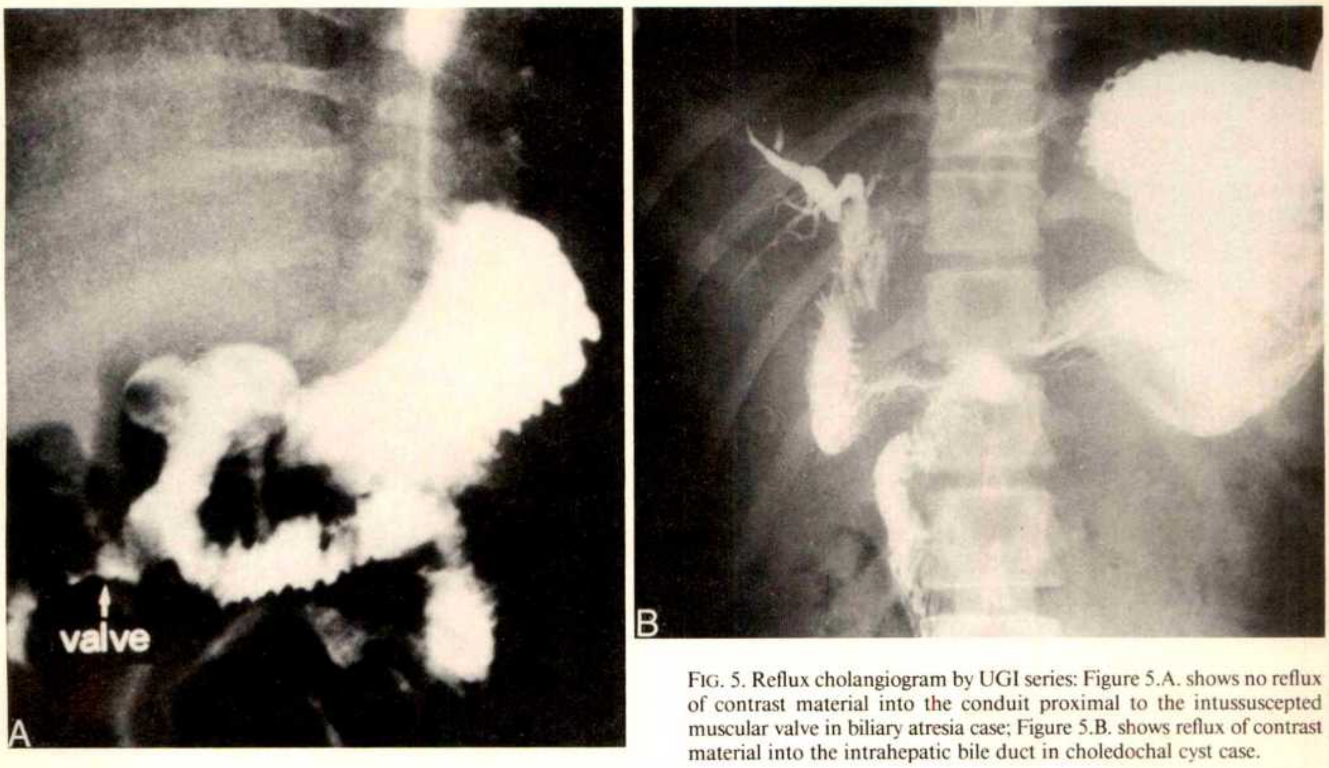

FIG. 5. Reflux cholangiogram by UGI series: Figure 5.A. shows no reflux of contrast material into the conduit proximal to the intussuscepted muscular valve in biliary atresia case; Figure 5.B. shows reflux of contrast material into the intrahepatic bile duct in choledochal cyst case.

as a consequence and persists for months after operation.[3] Cultures of fluid in the conduit from the area of the anastomosis at the porta hepatis *via* catheter reveal that the intestinal conduit is colonized by enteric flora within the first few weeks after the operation.[6,10–13] Both factors are present in most instances of hepatic portoenterostomy for biliary atresia and cholangitis after the Kasai operation merely compounds the pre-existing liver damage.

Another postoperative complication with high incidence and often serious results[14,15] is biliary obstruction caused by the granulation formed at the porta hepatis. Occurring in the early postoperative period, the features characteristic of biliary obstruction caused by granulation, as compared with those of ascending cholangitis, are the absence of infectious signs and the lack of response to medical treatment. In a survey of our patients, its incidence was 21% (8 of 39), and its mortality rate was 50% (4 of 8). Although bile flow was restored after the operative removal of the granulation in all cases, one half of the patients died of liver failure and other related complications. A reoperation to remove the granulation or scar tissue at the porta hepatis also is effective for intractable ascending cholangitis.[2] However reoperation for ascending cholangitis usually is done as a last resort because medical treatment is generally sufficient.

In hepatic portoenterostomy there is no mucosal continuity between the bile ducts and the intestinal wall, and the bile ducts open onto the cut surface of the remaining fibrous mass and hepatic parenchyma. Autoanastomosis occurs between the major intrahepatic duct epithelium and the coapted intestinal mucosa, a process that takes about 6 weeks.[15] If complications such as cholangitis and biliary obstruction caused by the granulation at the porta hepatis occur in this early postoperative phase, the transected microscopic ducts are prone to inflammatory closure. To prevent these complications, especially during this phase, the most effective means seems to be to prevent reflux of the intestinal contents to the porta hepatis. In the presence of reflux of intestinal contents, ascending cholangitis develops due to the exacerbation of bacterial contamination along with the rise in the biliary intraluminal pressure, and biliary obstruction caused by the granulation at the porta hepatis develops due to disturbances in healing of the hepatic portoenterostomy. Accordingly we took advantage of the valve mechanism of Vater's ampulla to prevent reflux of intestinal contents.

Hepatic portocholecystostomy for biliary atresia often has been performed to prevent postoperative cholangitis using the valve mechanism of Vater's ampulla. Ohi, Okamoto, and Kasai[16] reported that none of nine patients treated by this procedure developed postoperative cholangitis. Lilly also reported that none of four patients developed cholangitis after this procedure.[5] Although this procedure is simple and postoperative cholangitis is prevented, complications frequently occur, such as obstruction of the biliary conduit, bile leakage at the porta hepatis, and so on.[1,2,5] Furthermore the indication of hepatic portocholecystostomy is limited in number because it must be carried out in patients with a patent bile duct from gallbladder to duodenum.

TABLE 1. *Bacteriologic Study*

| Patient No. | Age at Operation (days) | Bacteria | Icterus | Cholangitis |
|---|---|---|---|---|
| 1 | 43 | *E. coli* $10^6$<br>Pseudomonas $10^5$ | – | – |
| 2 | 55 | — | – | – |
| 3 | 78 | — | – | – |
| 4 | 80 | *E. coli* $10^6$<br>Pseudomonas $10^7$ | + | – |
| 5 | 50 | Pseudomonas $10^7$ | – | + |
| 6 | 52 | Pseudomonas $10^6$ | – | – |
| 7 | 19 | Enterococcus $10^7$ | – | – |
| 8 | 30 | *E. coli* $10^5$ | – | – |

Our attempt is to construct an antireflux valve in the hepatic portoduodenal intestinal conduit. Jejunal interposition with this antireflux valve is effective in preventing ascending cholangitis and bile flow into the duodenum is enabled physiologically by this method. Postoperative roentgenograms showed no reflux of contrast material in the cases studied by upper GI series (Fig. 5A). Table 1 shows the types and concentrations of bacteria in the intestinal conduit. This finding indicates that the presence of bacteria is only one of several factors related to cholangitis. Although this antireflux valve may not be sufficiently tight to prevent flow of microorganisms in a retrograde manner, it prevents both reflux of intestinal contents and increase in the biliary intraluminal pressure and enables smooth bile flow in an anterograde manner through the valve. In a survey of our patients, the incidence of ascending cholangitis was 23% (9 of 39), and the mortality rate was zero (0 of 9). Compared with other procedures, our procedure had a decreased incidence of cholangitis and medical control was facilitated: the incidence of postoperative cholangitis in patients with bile drainage was 68% in the original Roux-en-Y, 56% in the double Roux-en-Y, 100% in the Roux-en-Y interposition, and 48% in the Suruga II.[2,4] Similar attempts to prevent cholangitis have been made. Kaufman and coworkers[17] used an isolated hepatic portoduodenal jejunal conduit with a 1-cm intussuscepted valve in seven cases with biliary atresia. Endo[18] used an ileocecal segment with a plicated ileocecal valve with good results.

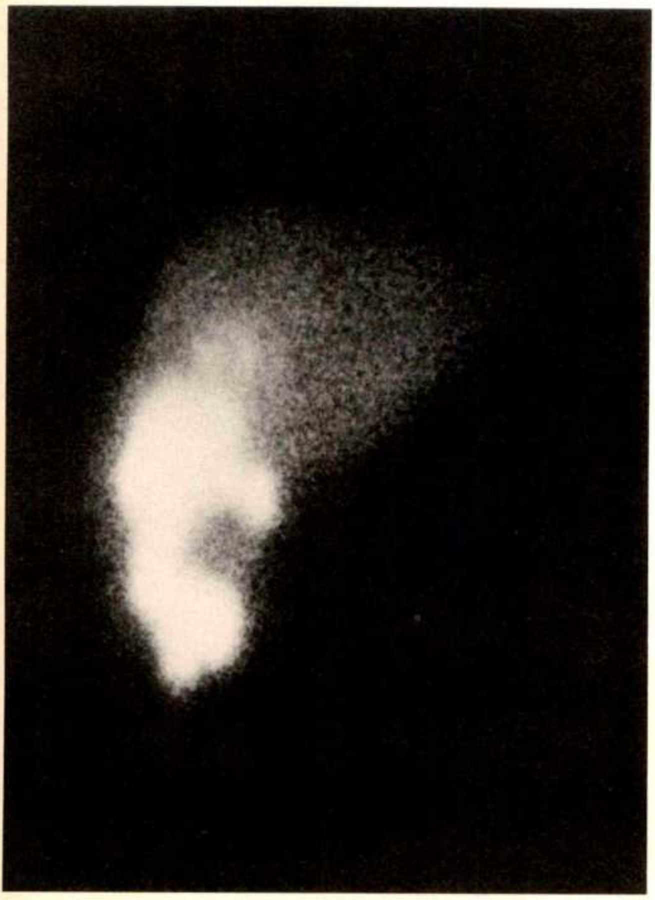

FIG. 6. Hepatobiliary scintigraphy, performed 45 minutes after injection of radioactive isotope, shows good hepatic uptake, normal excretion into the interposed jejunal conduit, and readiness of drainage into the duodenum through the valve.

At our institution we used an isolated jejunal conduit without valve in 45 patients with choledochal cyst and none of the patients developed postoperative cholangitis. X-ray studies showed the reflux of contrast material into the biliary tree in one half of the choledochal patients with hepatoduodenal intestinal conduit without valve (Fig. 5B). The difference in the incidence of postoperative cholangitis between biliary atresia and choledochal cyst suggests that adequate bile flow may be one of the most important factors in preventing cholangitis. However it takes considerable time to establish sufficient postoperative bile flow for biliary atresia. Therefore, in the early phase after obtaining bile drainage, it is necessary not only to prevent reflux of intestinal contents to the porta hepatis but also to increase the bile flow with choleretic agents.

Our 5-year jaundice-free survival rate of 64% is comparable to the 20% to 55% 5-year survival rates reported from other centers.[2,3,19–21] In conclusion our valved hepatic portoduodenal intestinal conduit decreased the incidence of cholangitis, facilitated medical control of cholangitis, and improved the survival rate.

## References

1. Kasai M, Suzuki S. A new operation for non-correctable biliary atresia—hepatic portoenterostomy. Shujutu 1959; 13:733–739
2. Ohi R, Hsnamatsu M, Mochizuki I, et al. Progress in the treatment of biliary atresia. World J Surg 1985; 9:285–293.
3. Lilly JR, Karrer FM, Hall RJ, et al. The surgery of biliary atresia. Ann Surg 1989; 210:289–296.
4. Miyano T, Ohya T, Kimura K, et al. Current state of the treatment of congenital biliary atresia. J Jpn Soc Surg 1989; 90:1343–1347.
5. Lilly JR. Hepatic portocholecystostomy for biliary atresia. J Pediatr Surg 1979; 14:301–304.

6. Tanaka K, Satomura K, Ohnishi S, et al. A new operation for treatment of biliary atresia—jejunal interposition hepatic portoduodenostomy with intestinal valve. J Jpn Soc Pediatr Surg 1980; 16:227–235.
7. Kasai M, Sawaguchi S, Akiyama H, et al. A proposal of new classification of biliary atresia. J Jpn Soc Pediatr Surg 1976; 12:327–331.
8. Lilly JR, Hitch DC. Postoperative ascending cholangitis following portoenterostomy for biliary atresia: measures for control. World J Surg 1978; 2:581–587.
9. Rothenberg SS, Schroter GPJ, Karrer FM, et al. Cholangitis after the Kasai operation for biliary atresia. J Pediatr Surg 1989; 24: 729–732.
10. Hitch DC, Lilly JR. Identification, quantification and significance of bacterial growth within the biliary tract after Kasai's operation. J Pediatr Surg 1978; 13:563–569.
11. Hitch DC, Lilly JR, Reller B, et al. Biliary flora and antimicrobial concentrations after Kasai's operation. J Pediatr Surg 1979; 14: 648–652.
12. Leblanc A, Lambert-Zechowsky N, Binge E, et al. Bacteriological analysis of jejunostomy fluid after surgery for extrahepatic biliary atresia. J Pediatr Gastroenterol Nutr 1983; 2:307–310.
13. Lilly JR, Hitch DC. Postoperative ascending cholangitis following portoenterostomy for biliary atresia: measures for control. World J Surg 1978; 2:581–587.
14. Takemoto H, Inomata Y, Matsukawa Y, et al. Icteric flare-up in patients with biliary atresia after hepatic portoenterostomy. Z Kinderchir 1988; 43:92–94.
15. Takemoto H, Tanaka K, Inomata Y, et al. Granulation at the porta hepatis following hepatic portoenterostomy for biliary atresia: the healing of experimental hepatoenterostomy. J Pediatr Surg 1989; 24:271–275.
16. Ohi R, Okamoto E, Kasai M. Some considerations of hepatic portocholecystostomy for the treatment of biliary atresia. Jpn J Pediatr Surg 1978; 10:983–989.
17. Kaufman BH, Luck SR, Raffensperger JG. The evaluation of a valved hepatoduodenal intestinal conduit. J Pediatr Surg 1981; 16:279–283.
18. Endo M, Katsumata K. Nonrefluxing draining conduit for biliary atresia—an intussuscepted ileocecal conduit and conduit duodenostomy. Jpn J Pediatr Surg 1985; 17:41–49.
19. Grosfeld JL, Fitzgerald JF, Predaina R, et al. The efficacy of hepatoportoenterostomy in biliary atresia. Surgery 1989; 106:692–700.
20. Houwen RHJ, Zwierstra RP, Severijnen RSVM, et al. Prognosis of extrahepatic biliary atresia. Arch Dis Child 1989; 64:214–218.
21. Kobayashi A, Itabashi F, Ohbe Y, et al. Long-term prognosis in biliary atresia after hepatic portoenterostomy: analysis of 35 patients who survived beyond 5 years of age. J Pediatr 1984; 105: 243–246.

# Surgical Management of 552 Carcinomas of the Extrahepatic Bile Ducts (Gallbladder and Periampullary Tumors Excluded)

## *Results of the French Surgical Association Survey*

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**Five hundred fifty-two cases of primary carcinoma of the extrahepatic bile ducts (gallbladder and periampullary tumors excluded) collected from 55 surgical centers were reviewed retrospectively. Three hundred seven patients (56%) had upper-third lesions (proximal carcinoma), whereas 71 (13%) and 101 (18%), respectively, had middle-third and lower-third bile duct carcinomas. The remaining patients had diffuse lesions. Resectability rates were 32% for upper-third localization compared to 47% and 51% for middle-third and lower-third localization, respectively. The operative mortality rate for proximal carcinomas was significantly lower with resection (16%) compared with palliative surgery (31%) ($p < 0.05$). Overall 1-year survival (operative deaths excluded) was 68% after tumor resection compared to 31% after palliative surgery ($p < 0.001$). Long-term results after surgical resection correlated with local and regional extension of the disease. The results of this study show that resection of extrahepatic bile duct carcinomas, particularly in an upper-third localization, often is associated with worthwhile long-term survival.**

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PRIMARY ADENOCARCINOMA OF the extrahepatic bile duct is an uncommon malignant tumor leading to progressive biliary obstruction, sepsis, secondary biliary cirrhosis, and hepatic failure. The neoplasm tends to grow slowly and to infiltrate surrounding structures such as liver parenchyma, intrahepatic bile ducts, and the hepatic pedicle. Metastases tend to develop late in the course of the disease.[1-3] However resectability rates and long-term survival rates remain low because of the difficulty of early diagnosis and the proximity of these tumors to vital structures.[3,4] Until recently palliative percutaneous, endoscopic, or surgical biliary drainage was considered acceptable treatment in terms of operative

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death and long-term survival when compared with more aggressive methods.[5–7] Survival rates after resection were related to local and distant tumor extension but remained matter for debate.[7–9] In 1979 a systematic approach to this condition showed a high resectability rate and an increased long-term survival.[10] To help clarify questions regarding optimal treatment, we analyzed the results of surgical management of 552 patients operated on for primary carcinoma of the extrahepatic bile ducts. These cases were collected in the French Surgical Association survey.

## Methods

The data concerning 552 patients operated on for extrahepatic bile duct carcinomas were collected through a retrospective survey that involved 55 surgical institutions principally in France (n = 43), but also in Algeria, Argentina, Belgium, Italy, Federal Republic of Germany, Switzerland, Tunisia, and Turkey. Twenty centers reported more than 10 cases and these centers accounted for 436 of the patients. The majority of the patients (89%) were treated after 1974, whereas the remaining patients (11%) were operated on between 1955 and 1974. Follow-up data were available for 485 patients (88%).

The data on the 552 cases were collected and analyzed on a Bull DPS 7 computer (Honeywell Bull, Angers, France). Comparisons of qualitative and quantitative parameters were achieved, respectively, by chi square and Student's t tests. Patient actuarial survival rates (excluding operative mortality) were presented using the Kaplan–Meier method, quantified by median, first and third quartiles, and differences were compared using the log rank sum test.

This study did not include patients with carcinoma of the ampulla of Vater, gallbladder, or intrahepatic cholangiocarcinoma. Furthermore benign lesions (adenoma or papilloma) as well as local extension or metastases of gastric, pancreatic, hepatocellular, and colon cancers were not considered. All the 552 patients reviewed were operated on for primary extrahepatic bile duct carcinoma (cholangiocarcinoma) according either to histologic analysis of resected or biopsied tumor (468 patients) or to the macroscopic and/or radiologic appearance of the biliary lesion when biopsy was considered a risky procedure for patients undergoing exploratory laparotomy or palliative biliary drainage only (84 patients). In these cases subsequent poor outcome and autopsy findings were used to confirm the diagnosis suspected at laparotomy. Local tumor extension, lymph node invasion, or distant metastases were staged according to the TNM classification for extrahepatic bile duct carcinomas.[11]

Among the 552 patients studied, 289 were men (52%) and 263 were women (48%). Mean age was 64.4 +/− 12.2 years. One hundred forty-four patients (26%) were noted to have associated gallstone disease. Lesions were classified as upper-, middle-, or lower-third tumors according to the American Joint Committee on Cancer.[11] Upper-third lesions were classified as type I, II, or III lesions.[12] Distribution of bile duct carcinomas by level is shown in Figure 1: 307 patients had upper-third lesions (type I, n = 60; type II, n = 89; type III, n = 158), 71 had middle-third lesions, and 101 had lower-third lesions. The tumors were diffuse in 73 patients.

Jaundice was the presenting feature in virtually all patients with the mean preoperative serum bilirubin level of 17.8 +/− 11.9 mg/dL. Other symptoms included weight loss (51%), abdominal pain (45%), fever (20%), and abdominal mass (10%). Preoperative diagnostic investigations consisted of abdominal echography in 386 patients (70%) and tomodensitometry in 101 patients (18%), as well as transhepatic or endoscopic retrograde cholangiography, respectively in 166 (30%) and 176 patients (32%).

### *Surgical Management*

Five hundred eleven patients (93%) were operated on as the initial therapeutic procedure, whereas in 41 patients (7%), surgery was performed after failure of percutaneous or endoscopic biliary drainage. The surgical management of the patients is summarized in Table 1. The overall resectability rate in the series was 34%, with 186 surgical resections performed compared to 366 palliative or exploratory operations. Resectability rates were 32%, 47%, 51%, and 6%, respectively, in upper-third, middle-third, lower-third, and diffuse carcinomas of the extrahepatic bile ducts. In 49 cases (mostly upper-third carcinomas), hepatic resection was combined with excision of the tumor. The type of hepatectomy was specified in 22 patients: 9 were right hepatectomies (with 7 extended to segment IV according to Couinaud),[13] 5 were left hepatectomies, 6 were resections of segment IV, and 2 were total hepatectomies with orthotopic liver transplantation. Middle-

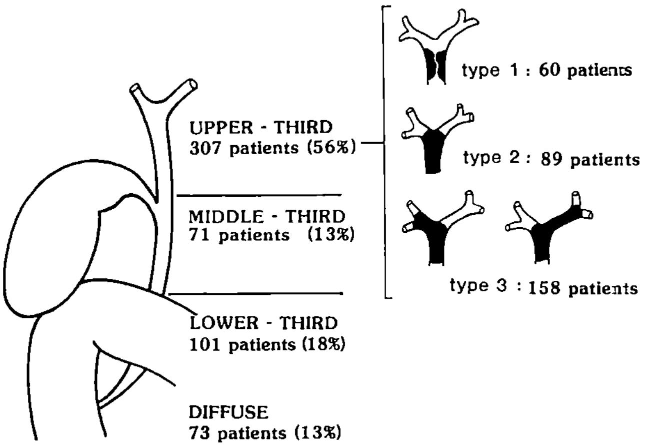

FIG. 1. Distribution of 552 primitive bile duct carcinomas by level, according to the classification of the American Joint Committee on Cancer[11] and, for upper-third carcinomas, to Bismuth and Corlette.[12]

TABLE 1. *Surgical Management in 552 Primary Carcinomas of the Extrahepatic Bile Ducts*

| Procedure | Upper-third Carcinomas (307 patients) | | Middle-third Carcinomas (71 patients) | | Lower-third Carcinomas (101 patients) | | Diffuse Carcinomas (73 patients) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Exploratory laparotomy | 31 | 10.1 | 4 | 5.6 | 7 | 6.9 | 21 | 28.8 |
| Surgical biliary drainage | | | | | | | | |
| Transtumoral intubation | 98 | 31.9 | 12 | 16.9 | 3 | 3 | 16 | 21.9 |
| Biliary-digestive anastomosis | 75 | 24.4 | 20 | 28.2 | 40 | 39.6 | 31 | 42.5 |
| External biliary drainage | 5 | 1.6 | 2 | 2.8 | | — | 11 | 1.4 |
| Resective surgery | | | | | | | | |
| Without hepatectomy | 51 | 16.6 | 31 | 43.7 | 51 | 50.5 | 4 | 5.5 |
| With hepatectomy | 47 | 15.3 | 2 | 2.8 | | — | | — |
| Resectability rate (%) | | 31.9 | | 46.5 | | 50.5 | | 5.5 |

third carcinomas usually were resected with reconstitution of biliary–intestinal continuity by hepatic–duodenal or hepatic-jejunal anastomosis. Resection of lower-third carcinomas, arising in the intrapancreatic portion of the common bile duct, was accomplished using a radical pancreaticoduodenectomy. Among the 303 palliative biliary drainage procedures, 166 were biliary–digestive anastomoses, 129 were transtumoral intubations, and 8 were external biliary drainages. The type of biliary–digestive anastomosis was known in 88 observations: 27 were intrahepatic anastomoses, 31 were hepaticoduodenostomies, 26 were hepaticojejunostomies, and 2 were cholecystoduodenostomies. In two cases hepatodigestive anastomoses were performed, either with the stomach (Dogliotti procedure) or with the jejunum (Longmire procedure). Similarly, among the 20 cases of documented intrahepatic–digestive anastomoses with Roux-en-Y loops, 15 were performed to the duct of the left anterolateral segment (segment III) according to the technique described by Bismuth et al.,[5,12] 4 were to right ducts, and 1 consisted of anastomoses to left and right biliary ducts.

## Results

Comparative analysis of patients treated by resective or palliative surgery showed that resected patients were significantly younger (62 +/− 12 years) than nonresected patients (66 +/− 12 years: $p < 0.05$). Similarly the incidence of chronic respiratory disease, cardiac insufficiency, and cirrhosis was significantly higher in nonresected patients ($p < 0.05$ for each of the three comparisons).

The overall 30-day hospital (operative) mortality rate was 26%. The operative mortality rate according to the type of surgical management is detailed in Table 2 for the three levels of localized bile duct carcinoma and in Table 3 for upper-third biliary tumors. In upper-third tumors, the mortality rate was statistically higher after exploratory or decompressive surgery than after tumor resection. For diffuse carcinomas the operative mortality rates were 45% (9 of 20) after exploratory surgery, 36% (5 of 14) after transtumoral intubation, 25% (6 of 24) after biliary digestive anastomosis, and 33% (1 of 3) after resective surgery. Interestingly, among 38 patients operated on following failure of nonoperative biliary drainage, the operative mortality rate was 39% (10 of 26) after palliative surgery, whereas no resected patient (0 of 12) died after operation in this group ($p < 0.05$). Before 1974 the resectability rate for upper-third tumors in this series was 10%. From 1974 to 1987, the resectability rate was 51%. The resectability

TABLE 2. *Operative Mortality in 425 Extrahepatic Bile Duct Carcinomas According to Surgical Management and Tumor Location*

| Carcinoma | Surgical Resection | Palliative Biliary Drainage |
|---|---|---|
| Upper-third Carcinomas | 28/181 (15.5%) | 30/97 (30.9%)* |
| Middle-third Carcinomas | 7/31 (22.6%) | 6/32 (18.8%)† |
| Lower-third Carcinomas | 12/46 (26.1%) | 7/38 (18.4%)† |

* $p < 0.01$ when compared to resection for the same tumor location.
† Not significant when compared to resection for the same tumor location.

TABLE 3. *Operative Death in 278 Patients with Upper-third Bile Duct Carcinomas According to the Type of Surgery*

| Surgery | | Operative mortality | | |
|---|---|---|---|---|
| Exploratory (n = 24) | | 58.3% | | |
| Transtumoral intubation (n = 88) | NS | 27.3% | | p < 0.01 |
| Biliary digestive anastomosis (n = 69) | | 26.1% | | |
| | | | p < 0.05 | |
| Resective surgery | | | | |
| With hepatectomy (n = 50) | NS | 14.0% | | |
| Without hepatectomy (n = 47) | | 17.0% | | |

NS, not significant.

TABLE 4. *Long-term Patient Survival (Excluding Operative Death) According to Bile Duct Carcinoma Location and Type of Surgery*

| | Resection | | Palliative Surgery | |
|---|---|---|---|---|
| Location | n | Survival* | n | Survival* |
| Upper third | | | | |
| Type 1 | 14 | 16 (9–39) | 22 | 5 (3–9)† |
| Type 2 | 22 | 24 (11–38) | 42 | 9 (3–15)‡ |
| Type 3 | 46 | 23 (11–34) | 65 | 10 (5–15)‡ |
| Middle third | 25 | 13 (8–47) | 27 | 9 (4–13)§ |
| Lower third | 34 | 64 (7–69) | 36 | 8 (4–13)‡ |

* Median (first and third quartiles) patient survival (months).
† Not significant when compared to resection.
‡ $p < 0.001$ when compared to resection.
§ $p < 0.05$ when compared to resection.

rate also varied from center to center, with a range of 0% to 60%. Overall median survival (excluding operative deaths) was 11 months (first quartile, 5 months; third quartile, 24 months). Considering all tumor levels, median survival was 23 months (10 to 45 months) for resective surgery (n = 143 patients) compared to 8 months (3 to 14 months) after palliative surgery (n = 230 patients) ($p < 0.001$). Survival rates according to surgical management and lesion level are detailed in Table 4, which shows that survival after surgical resection of extrahepatic bile duct carcinoma was longer for all tumor levels, and the only level in which the trend did not reach statistical significance was type I upper-third tumors. In upper-third cancers, median long-term survival time was similar with or without hepatic resection (respectively, 24 months *versus* 23 months; not significant [NS]).

For palliative surgery of upper-third bile duct carcinomas, median long-term survival was statistically similar after either surgical transtumoral intubation (n = 64 patients) or biliary–digestive anastomosis (n = 51 patients), respectively, 9 months (5 to 15) compared to 9 months (5 to 19) (Fig. 2). For the 28 patients operated on after failure of nonoperative biliary drainage in which data were available in regard to their long-term follow-up, survival was statistically similar, whatever the type of surgical management, resective or palliative (median survival respectively 8 months (n = 12) *versus* 10 months [n = 16]; NS).

The effect of local tumor extension on survival is given in Figure 3: median survival time after surgical resection of an extrahepatic bile duct carcinoma, wherever located, was 64 months (13 to 101) for T1 stage (n = 16 patients), 23 months (8 to 45) for T2 (n = 43 patients), 18 months (10 to 37) for T3 (n = 54 patients), and 18 months (3 to 18) for T4 (n = 12 patients). Similarly absence of lymph node involvement statistically improved median survival: 20 months (12 to 45) for N0 *versus* 9 months (5 to 20) for N+ ($p < 0.001$). The presence of hepatic metastases worsened the prognosis with median survival of 12 months (5 to 25) for M0 patients *versus* 6 months (3 to 15) for M+ ($p < 0.001$).

Concerning adjunctive therapy external irradiation was administered after operation in 27 cases. Long-term survival was similar after tumor resection with or without irradiation. Similarly there was no significant difference in the median survival time after palliative surgery with postoperative radiotherapy compared to surgery without irradiation, although there was a trend toward longer sur-

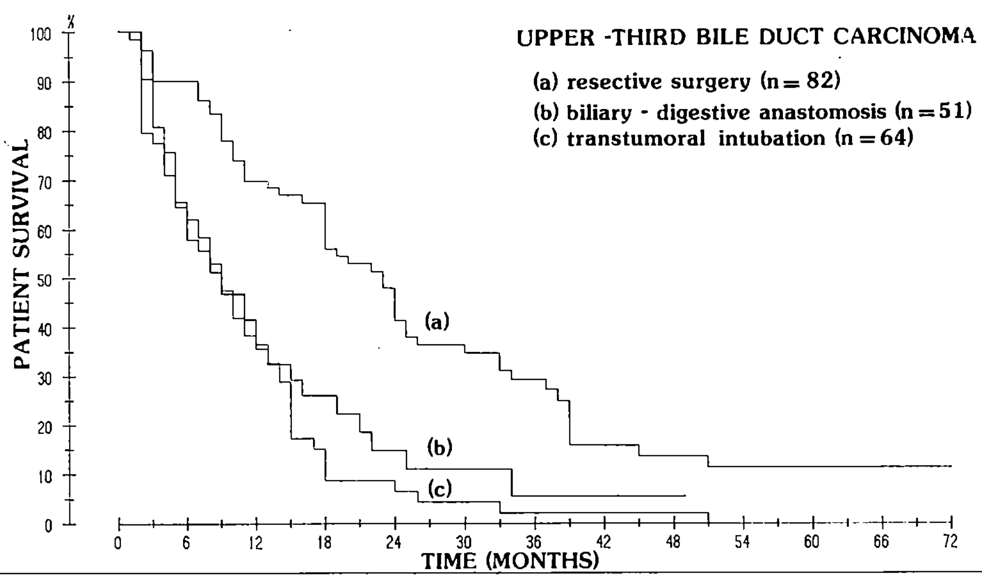

FIG. 2. Survival curves (operative death excluded) in patients operated for upper-third bile duct carcinoma according to the type of surgical management: (a) resective surgery (n = 82); (b) biliary-digestive anastomosis without resection (n = 51); (c) transtumoral intubation (n = 64). Statistical significance: (a) *vs.* (b): $p < 0.001$; (a) *vs.* (c): $p < 0.001$; (b) *vs.* (c): NS.

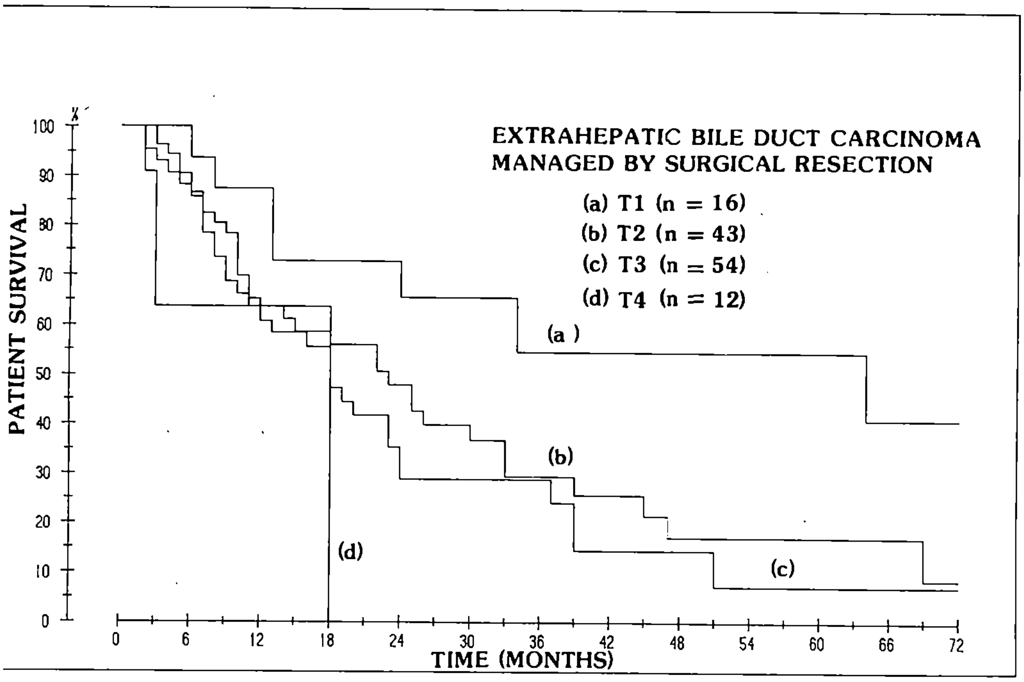

FIG. 3. Survival curves (operative death excluded) in 125 patients with extrahepatic bile duct carcinoma managed by surgical resection, according to local extension of the tumor: (a) T1 (n = 16); (b) T2 (n = 43); (c) T3 (n = 54); (d) T4 (n = 12). T staging was determined according to the classification of the American Joint Committee on Cancer.[11]

ival in the irradiated group: respectively, 8 months (3 to 4) *versus* 13 months (11 to 35): $0.10 < p < 0.05$.

## Discussion

Resectability rates reported for carcinoma of the extra-.epatic bile ducts have been low in most series, particuırly for upper-third carcinoma.[8,14,15] These low rates are .ue, in part, to late diagnosis and the technical difficulty f resection of this area. The variability of resection rates etween centers in this series together with the trend overll to increased rates suggests that certain centers are reɜcting these lesions because of increased technical exertise in the area. The data presented here show that if ırgical resection can be accomplished, the patient is more kely to have a long-term survival.

In considering operative mortality after surgery for uper-third carcinoma, mortality rates were lower in the :oup having resection. There are no doubt several reasons ɔr this. First the patients tended to be younger and more hysically fit in the resection group and their diseases ould often be less far advanced. The fact that resections :nded to be carried out in centers with special expertise ı the surgery of this area also may have been another :ason for the lower mortality rate in the resection group. lso the patients in this group had their malignant tumors :moved, although the beneficial effect this has on postɔerative mortality remains unknown. However this im-·ovement with resection was not seen in patients with ımors of the middle- and lower-third of the bile duct 'able 2). This may be explained by the technical ease ith which biliary decompression is achieved with tumors in these locations. Nevertheless the operative mortality rate after resection of middle- and lower-third cancers reported here is probably unacceptable by present standards, but the study has collected data dating back to 1954. Now, in centers with a special interest in hepatobiliary diseases, the operative mortality rate after the Whipple procedure should be less than 5%.[15,16] In the present study, the operative mortality rate was similar, regardless of whether hepatic resection was combined with surgical excision, as was the long-term survival. It is clear that the prognosis does not depend on the type of resection (with or without hepatectomy) but on tumor location (Table 4) and on local extension of the neoplasm, according to the TNM classification (Fig. 3).

However, despite better results and current technical progress,[10,17] the removal of extrahepatic bile duct carcinomas, especially upper-third lesions, still often proves impractical. Then palliative treatment is the only feasible solution and this proved to be the case in 66% of the patients in this survey. The aim of palliative treatment is to eliminate jaundice, relieve pruritus and sometimes pain, and to prevent the complications of biliary retention in the hope of increasing the duration and, above all, the comfort of survival.[2,5] According to the data presented here for upper-third carcinoma, results of both types of surgical palliation (transtumoral intubation or biliary-digestive anastomosis) were similar, achieving an operative mortality rate of about 27% and a median survival time of about 9 months. However, due to the retrospective nature of this multicenter study, comparison of quality of survival between the two palliative techniques was not performed. In contrast with these data, results from the literature on surgical palliation in patients with unresectable proximal tumors suggest that the mortality rate of surgical transtumoral intubation is lower than after biliary–digestive bypass.[2,18] Opposite results were published recently by Bismuth and colleagues[14] with operative mortality rates of 7% in patients having biliary drainage compared to 30% in the surgical intubation group, with a significantly worse quality of survival in the latter patients. Whichever palliative technique is used, it is important to remember that both procedures carry a significant operative mortality rate. Nonsurgical biliary decompression modalities through either the transhepatic or the endoscopic route are now available. However their results in terms of incidence of recurrent cholangitis and the relative roles of surgical bypass and endoscopic stenting remain controversial.[19,20] Devière[19] recently showed that in upper-third cancers, the nonsurgical biliary decompression patients have a much lower 30-day mortality rate and a longer survival time when both hepatic lobes are drained, especially in types II and III carcinomas. Furthermore, in a randomized trial concerning 52 jaundiced elderly patients with malignant obstruction of the distal bile duct, Shepherd and colleagues[21] noted a shorter initial hospital stay but more readmissions in the endoscopically drained group when compared to the conventional surgical bypass group. Obviously the question of the best palliative therapy is not elucidated when analyzing the available data.

In conclusion the results of the French Surgical Association survey showed that the prognosis of primary extrahepatic bile duct carcinomas depends on the location of the tumor as well as the local and regional extension according to the TNM classification. Operative mortality rate and long-term survival was better after tumor resection when compared with palliative surgical biliary drainage. However the latter procedure tends to be undertaken in a higher-risk subpopulation of patients with unresectable disease. In upper-third bile duct carcinomas, operative mortality rate and long-term survival were not influenced by performance of combined hepatectomy with tumor resection. For the same location, long-term patient survival after surgical transtumoral intubation was statistically similar to biliary digestive anastomosis. This suggests that, in cases of unresectability, endoscopic or transhepatic intubation of both lobes may be preferable to surgery. Nevertheless this still begs the question of defining unresectability without operation. However whether nonsurgical transtumoral intubation offers a similar or better quality of life to biliary–digestive anastomosis was not determined in this surgical survey and remains to be demonstrated in a prospective trial.

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## References

1. Beazley RM, Hadjis N, Benjamin IS, Blumgart LH. Clinicopathological aspects of high bile duct cancer. Experience with resection and bypass surgical treatments. Ann Surg 1984; 199:623–636.
2. Lai ECS, Tompkins RK, Roslyn JJ, Mann LL. Proximal bile duct cancer. Quality of survival. Ann Surg 1987; 205:111–118.
3. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis: an unusual tumor with distinctive clinical and pathological features. Am J Med 1965; 38:241–256.
4. Todoroki T, Okamura T, Fukao K, et al. Gross appearance of carcinoma of the main hepatic duct and its prognosis. Surg Gynecol Obstet 1980; 150:33–40.
5. Traynor O, Castaing D, Bismuth H. Left intrahepatic cholangioenteric anastomosis (round ligament approach): an effective palliative treatment for hilar cancers. Br J Surg 1987; 74:952–954.
6. Cotton PB. Duodenoscopic placement of biliary prostheses to relieve malignant obstructive jaundice. Br J Surg 1980; 69:501–503.
7. Leung JWC, Emery R, Cotton PB, et al. Management of malignant obstructive jaundice at the Middlesex Hospital. Br J Surg 1983; 70:584–586.
8. Langer JC, Langer B, Taylor BR, et al. Carcinoma of the extrahepatic bile ducts: results of an aggresive surgical approach. Surgery 1985; 98:752–759.
9. Evander A, Fredlund P, Hoevels J, et al. Evaluation of aggressive surgery for carcinoma of the extrahepatic bile ducts. Ann Surg 1980; 191:23–29.
10. Launois B, Campion JP, Brissot P, Gosselin M. Carcinoma of the hepatic hilus. Surgical management and the case for resection. Ann Surg 1979; 190:151–157.
11. American Joint Committee on Cancer. Extrahepatic bile ducts (exclusive of ampulla and intrapancreatic bile duct). *In* Manual for Staging of Cancer, Second Edition. Philadelphia: JB Lippincott, 1983, pp 91–94.
12. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet 1975; 140:170–178.
13. Couinaud C. Lobes et segments hépatiques. Notes sur l'architecture anatomique et chirurgicale du foie. La Presse Médicale 1954; 62: 709–712.
14. Bismuth H, Castaing D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. World J Surg 1988; 12:39–47.
15. Tompkins RK. Treatment and prognosis in bile duct cancer. World J Surg 1988; 12:109–110.
16. van Heerden JA. Pancreatic resection for carcinoma of the pancreas: Whipple versus total pancreatectomy—an institutional perspective. World J Surg 1984; 8:880–888.
17. Mizumoto R, Kawarada Y, Suzuki H. Surgical treatment of hilar carcinoma of the bile duct. Surg Gynecol Obstet 1986; 162:153–158.
18. Terblanche J, Kahn D, Bornman PC, Werner D. The role of U tube for palliative treatment in high bile duct carcinoma. Surgery 1988; 103:624–632.
19. Devière J, Baize M, Buset M, et al. Complications of internal biliary drainage. Acta Endoscopica 1986; 16:19–29.
20. Yamakawa T, Essuerra RD, Kaneko H, Fukuma E. Percutaneous transhepatic endoprosthesis in malignant obstruction of the bile duct. World J Surg 1988; 12:78–84.
21. Shepherd HA, Poyle G, Ross APR, et al. Endoscopic biliary endoprosthesis in the palliation of malignant obstruction of the distal bile duct. A randomized trial. Br J Surg 1988; 75:1166–1168.

# Colectomy, Mucosal Proctectomy, and Ileal Pouch–Anal Anastomosis

## *A Prospective Trial of Optimal Antibiotic Management*

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**The ideal prophylactic antibiotic regimen has not been established for patients undergoing colectomy, mucosal proctectomy, and endorectal ileoanal anastomosis, a prolonged operation frequently accompanied by abdominal and pelvic contamination and associated with an infection rate up to 20%. The aim of this study was to evaluate, in a prospective, randomized, double-blind fashion, the efficacy of a short perioperative course compared to an extended postoperative course of intravenous antibiotics cefoxitin) in patients undergoing colectomy with ileoanal anastomosis. Forty patients with ulcerative colitis or familial polyposis coli received a mechanical and oral antibiotic bowel preparation and a standard three-dose perioperative course of intravenous cefoxitin. Patients then were randomized to receive ntravenous cefoxitin, 1 g every 6 hours, or placebo for 5 days. No differences in overall postoperative morbidity were observed and neither group developed intra-abdominal, pelvic, or wound nfections. It is concluded that a standard three-dose perioperative course of intravenous antibiotics provides adequate prophylaxis n the prevention of infectious complications in patients undergoing colectomy, mucosal proctectomy, and ileoanal anastomosis.**

COMBINED COLECTOMY, MUCOSAL PROCTECTOMY, and endorectal ileal pouch–anal anastomosis is a major surgical alternative for patients with chronic ulcerative colitis or familial polyposis coli who require colectomy. Infection rates of 10% to 20% are eported, despite the use of mechanical bowel preparation and preoperative oral antibiotic regimens.[1–4] Parenteral antibiotics are added to the vigorous mechanical bowel preparation along with oral antibiotics as the prophylatic egimen at many medical centers.[5] The duration of the parenteral prophylactic agent has been reported to be as ong as 5 days after operation in some instances. While here is little evidence to support this prolonged postoprative antibiotic regimen, the rationale cited has been that the gross spillage of rectal intraluminal contents into the pelvis, which occurs frequently during the rectal mucosal dissection, converts the operation from a clean contaminated category into a grossly contaminated one. Operations in this latter category are associated with significantly higher rates of pelvic and wound infections.[6] Furthermore pelvic infections after ileal pouch–anal anastomosis may result in loss of the ileal pouch and require conversion to a permanent abdominal ileostomy.

In our own initial clinical experience with 40 consecutive patients undergoing ileal pouch–anal anastomosis,[7] no pelvic or wound infections occurred. All of these patients were given a mechanical and oral antibiotic (neomycin and erythromycin base) bowel preparation and then received a preoperative broad-spectrum antibiotic (cefoxitin) that was continued for 5 postoperative days. While a prolonged course of antibiotics may decrease the risk of pelvic infection after ileoanal anastomosis, it also may increase the risk of superinfection and adds considerably to patient costs. Thus the ideal prophylactic antibiotic regimen for patients undergoing ileal pouch–anal anastomosis has not been established clearly. Our aim, therefore, was to study, in a prospective, double-blind, randomized fashion, the efficacy of a short perioperative course *versus* an extended postoperative course of intravenous antibiotics in patients undergoing colectomy, mucosal proctectomy, and ileal pouch–anal anastomosis.

## Methods

### *Patient Selection*

Forty patients with a clearly established diagnosis of chronic ulcerative colitis, familial polyposis, or Gardner's

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syndrome who required colectomy and who were candidates for mucosal proctectomy with ileal pouch–anal anastomosis were entered into the study during a period of 9 months. Patients were excluded for the following reasons: (1) allergy to penicillin or cephalosporin; (2) antibiotic use within 1 week before the operation; (3) mechanical bowel obstruction or any other functional or anatomic reason precluding mechanical bowel preparation; or (4) the presence of an existing ileostomy or colostomy. Written informed consent was obtained and Institutional Review Board approval was received in conformance with guidelines for research with human subjects at the University of Utah Health Science Center.

### *Patient Management*

All patients were prepared for surgery with (1) a clear liquid diet for 4 days before surgery; (2) mechanical bowel preparation consisting of 300 mL of oral magnesium citrate and two tap water enemas administered on preoperative day 2 and 300 mL of oral magnesium citrate and tap water enemas until clear administered on preoperative day 1; (3) oral antibiotic preparation consisting of 1 g neomycin and 1 g erythromycin base by mouth at 1:00 P.M., 2:00 P.M., and 11:00 P.M. on preoperative day 1; (4) 2 g cefoxitin administered intravenously during a 20-minute period immediately before surgery, with additional 2 g intravenous doses of cefoxitin given at 6 hours and 12 hours after the initial dose.

All surgeries were performed in a standard fashion by a single surgeon.[7] The rectum was irrigated with 200 mL of a povidine-iodine solution *via* a transanal rectal catheter. The skin of the abdomen, perineum, and lower extremities was prepared with alcohol and povidine-iodine. Following abdominal colectomy, rectal mucosal dissection was begun at the pelvic peritoneal reflection and carried to the level of the levator ani sling. A 15-cm ileal J pouch then was constructed. The patient was placed in a modified lithotomy position, the rectal mucosal cuff everted, and the mucosal dissection completed. The ileal J pouch then was brought into the pelvis endorectally and the ileal pouch–anal anastomosis completed. The patient was taken out of the lithotomy position and an active closed drainage catheter positioned between the ileal pouch and the rectal muscular cuff and brought out through the abdominal wall *via* a left lower abdominal stab wound. The abdomen was irrigated with 4000 mL of normal saline. Forty cm proximal to the ileal pouch, a loop of bowel was identified, brought out through the right lower abdominal wall, and suspended over a stomal rod. The fascia and skin were closed and isolated before opening of the ileum and construction of the loop ileostomy. The precise times of antibiotic delivery and of each critical phase of the operation were recorded. Total blood loss and transfusion requirements also were recorded. The number of entries through the rectal mucosa into the lumen of the rectum was recorded together with an assessment by the surgeon of the amount of contamination occurring with each entry. This was scored on a scale rating from 0 (no contamination) to 4+ (major contamination).

### *Study Design*

In the recovery room, patients were randomized into one of two treatment groups: group A—cefoxitin, 1 g in 10 mL of 5% dextrose in water infused intravenously by a Bard infusion pump (Travenol Labs, Inc., Deerfield, MI) over a period of 20 minutes every 6 hours for 5 days, beginning 6 hours after the fixed postoperative dose; or group B—placebo, 10 mL of 5% dextrose in water administered in a similar manner as group A.

Patients were otherwise managed according to a standard postoperative protocol.[7] The surgeon, nurse, and wound observers were blinded as to the randomization group.

### *Evaluation*

The patient's general clinical status was assessed by the surgical house staff and attending surgeon. Clinical and laboratory data were recorded daily by the clinical coordinator. Maximum temperature in each 24-hour period was recorded and fever defined as a temperature greater than 38 C after postoperative day 2. Any elevation in white blood cell count of two or more times the preoperative level, with or without a left shift in the cell differential, was recorded. Other systemic physical signs of infection such as tachycardia, ileus, abdominal tenderness on physical examination, perineal drainage, or tenderness were recorded.

By definition a wound was considered uninfected if it was healing without evidence of erythema or discharge. Wounds were considered infected if purulent drainage was present, regardless of culture results or if nonpurulent material contained pathogenic bacteria. Each wound infection was classified as (1) deep, with infection extending below the fascia; or (2) moderate, when deep subcutaneous tissues were involved. Wounds were considered possibly infected if there was evidence of induration and inflammatory changes of the skin but without purulent discharge. The patient was examined daily for physical signs of intra-abdominal infection with confirmation by computed tomography.

Other sources of infectious morbidity were monitored, including pneumonia and urinary tract infections. Pneumonia was documented by purulent sputum and mod-

:rate to abundant bacterial growth from the sputum in he presence of radiographic changes suggestive of pneunonia. Urinary tract infection was documented by a bacerial colony count of more than $10^5$ organisms per miliiter from a properly obtained specimen unless a repeat :ulture before the institution of antibiotics did not confirm ›acteruria.

All other noninfectious complications were recorded .nd any complications that could be directly attributed o the use of cefoxitin were documented carefully. This pecifically included any allergic reactions, including rash ›r signs of hypersensitivity and renal toxicity. All patients vere seen in the outpatient clinic 2, 4, and 8 weeks after lischarge from the hospital to identify any long-term omplications resulting from the protocol. Physical findngs and wound status were recorded at each outpatient isit. Eight weeks after ileal pouch–anal anastomosis, the ɔop ileostomy was closed. Patients then were followed at , 3, 6, 9, and 12 months after ileostomy closure.

The groups were compared for differences in operative ata, hospitalization, and postoperative complications sing chi square analysis. Statistical difference was defined s $p < 0.05$. The number of patients to be recruited into ıe study to show a difference between groups was deterıined by power analysis.[8]

## Results

Patient demographics are shown in Table 1. Forty paents were entered into the study, with 18 randomized ) receive perioperative cefoxitin and postoperative ce)xitin for 5 days (group A) and 22 randomized to receive erioperative cefoxitin and then placebo for 5 days (group ). The two study groups were statistically comparable ›r sex, age, and diagnosis. The mean ± SEM operating me (5.3 ± 0.2 hours for group A and 5.1 ± 0.2 hours ›r group B) did not differ (Table 2). No difference was bserved in the mean blood loss (659 ± 4 mL for group . and 773 ± 02 mL for group B). The overall incidence f entry into the bowel lumen during rectal mucosal dis:ction was greater in group A (50%) than in group B !7%), but the incidence of major contamination was the ıme (22% *versus* 23%). As would be expected, the cost f 5 days of antibiotics was greater for the long course ıan for the short course ($586 *versus* $66).

TABLE 1. *Study Population*

| Data | Group A (CFX) (n = 18) | Group B (placebo) (n = 22) |
|---|---|---|
| ale:female ratio | 9:9 | 12:10 |
| ean ± SEM age (yrs) | 35.8 ± 8.3 | 30.3 ± 2.4 |
| C:polyposis ratio | 16:2 | 18:4 |

TABLE 2. *Operative Data*

| Data | Group A (CFX) (n = 18) | Group B (Placebo) (n = 22) |
|---|---|---|
| Operating time (hrs) | 5.3 ± 0.2* | 5.1 ± 0.2 |
| Blood loss (mL) | 659 ± 64 | 773 ± 92 |
| Entries into lumen | 9/18 (50%) | 6/22 (27%) |
| Major contamination (>2+) | 4/18 (22%) | 5/22 (23%) |
| Transfusion requirement | 9/18 (50%) | 13/22 (59%) |
| >1 U transfusion | 5/18 (28%) | 8/22 (36%) |

* Mean ± SEM.

Clinical results are shown in Table 3. No intra-abdominal, pelvic, or wound infections were observed in either group. Six patients (33%) in group A experienced postoperative complications, as did four patients (18%) in group B. One patient in each group experienced a rash. In the patient in group A, cefoxitin was discontinued. Five patients in group A were febrile after postoperative day 2 as compared to nine patients in group B. This was not statistically different and the elevated temperatures did not appear to be clinically significant. White blood cell count, blood urea nitrogen, and serum creatinine values did not differ between groups. Total hospitalization for the two groups did not differ with a mean length of hospitalization of 8.4 ± 0.2 days in group A and 8.7 ± 0.4 days in group B. Episodes of ileal pouch dysfunction or pouchitis were recorded. Pouchitis is a nonspecific inflammation of the ileal pouch mucosa with clinical manifestations of increased stool frequency with urgency, liquid stools, and abdominal cramps, which responds in most cases to a course of metronidazole.[7] The incidence of pouchitis significantly differed between the two groups, with no cases in group B and seven cases in group A ($p < 0.01$). These episodes were observed between 1 and 12 months after ileostomy closure.

## Discussion

The optimal method of reducing infectious complications after colon and rectal resection is controversial. In-

TABLE 3. *Clinical Data*

| Data | Group A (CFX) (n = 18) | Group B (Placebo) (n = 22) |
|---|---|---|
| Infections | | |
| Wound | 0/18 (0%) | 0/22 (0%) |
| Intra-abdominal | 0/18 (0%) | 0/22 (0%) |
| Febrile after postop. day 2 | 5/18 (28%) | 9/22 (41%) |
| Rash | 1/18 (6%) | 1/22 (5%) |
| Elevated WBC 2X preop. | 9/18 (50%) | 4/22 (18%) |
| Elevated creatinine or BUN | 1/18 (5%) | 0/22 (0%) |
| Noninfectious complications | 6/18 (33%) | 4/22 (18%) |

BUN, blood urea nitrogen.

fection rates with mechanical preparation of the bowel alone without any type of antibiotic prophylaxis have been reported to be as high as 50% to 75%.[9] Several controlled, prospective, randomized clinical trials provided convincing support for the use of antibiotic prophylaxis in colon and rectal operations. These studies have provided specific supportive data about the efficacy of oral antibiotic administration when combined with preoperative mechanical preparation of the colon.[10,11]

The role of intravenous prophylactic antibiotics in colorectal operations remains unclear.[11-14] Parenteral antibiotics had appeared to be of little value until the study of Polk and Lopez-Mayor,[15] a prospective, double-blind, randomized trial that demonstrated that intravenous antibiotics administered before operation could significantly reduce infection without the addition of an oral antimicrobial agent. Infection occurred in only 5% of patients having colon operations.

Another prospective, double-blind, randomized study demonstrated that antibiotics begun before operation failed to reduce the rate of infection to less than control cases given a parenteral placebo alone.[5] The critical issue appeared to be the availability of antibiotic in tissues and blood at the time of bacterial challenge. Antibiotics administered later had little or no effect because they were delivered to the site of contamination well beyond the relevant period. In another study, continuation of antibiotics beyond the closure of the skin incision resulted only in extra expenditure; no additional benefit could be demonstrated.[15] However, with some prolonged and complex gastrointestinal operations, particularly in pediatric patients, the tendency has been to continue antibiotics for 2 to 7 days after operation.[5]

Whether parenteral antibiotics are indicated if the patient receives oral antimicrobial therapy remains controversial. Aminoglycosides are poorly absorbed from the intestine, about 3% to 5%; and both erythromycin and metronidazole are absorbed to varying extents. In one study the addition of a parenteral agent added nothing; however the dose used may not have been adequate.[11] Another study, however, demonstrated that parenteral antibiotics begun before operation significantly reduced infection rates despite the use of an oral antimicrobial preparation.[5] Parenteral administration of the antibiotic to achieve tissue concentrations before the time of bacterial challenge appears to be the most important factor.[16]

The half-life of the drug in relation to the length of the operation may be critically important. Kaiser et al.[17] reported higher infectious complication rates in patients with operation times exceeding 4 hours. In this study oral antibiotics were not included in the preoperative bowel preparation of the patients in the antibiotic (cefoxitin)-treated group. Recently we examined the pharmacokinetic disposition of cefoxitin in patients undergoing colectomy, mucosal proctectomy, and ileal pouch–anal anastomosis.[18] It was found that if the antibiotic was administered 'on call' to the operating room, a mean time of 112 minutes elapsed between administration of drug and time of surgical incision. With the relatively short half-life of the antibiotic, most of the antibiotic in plasma was eliminated by the time of skin incision, and certainly several hours later at the time of maximal contamination. Furthermore antibiotic dispensation was found to be markedly altered by such factors as fluid balance, blood loss at operation, use of a large volume of peritoneal irrigation fluid, and the use and timing of an intraoperative dose of antibiotics. Therefore, when oral antibiotics are not used, a parenteral antibiotic plasma concentration exceeding a critical level for a sufficient duration may be needed to prevent infectious complications.

The most efficacious and safest antibiotic regimen for patients undergoing colectomy, mucosal proctectomy, and endorectal ileoanal anastomosis has not been established clearly. The operation is performed on high-risk patients with chronic inflammatory disease of the bowel who have been treated frequently with chronic corticosteroids. The operation itself is long (4 to 7 hours), technically difficult, and associated not infrequently with gross spillage of intraluminal contents into the pelvis. In many centers, therefore, the standard regimen of bowel preparation and prophylaxis against infection has included mechanical cleansing of the bowel, oral antibiotics and perioperative intravenous antibiotics that are continued for 2 to 7 days after surgery. With this type of regimen used in 40 patients undergoing ileal pouch–anal anastomosis, we had no intra-abdominal or wound infections.[7] However, because of the expense, potential risk and lack of data supporting such a long course of antibiotics, we wondered if a standard perioperative course of intravenous antibiotics would be adequate. In this prospective, double-blind, randomized study of a short perioperative course compared to an extended postoperative course of intravenous antibiotics in patients undergoing colectomy with ileal pouch–anal anastomosis, we demonstrated no difference in the incidence of infectious complications. The long course of antibiotics was significantly more expensive but was not associated with a higher antibiotic complication rate. Of importance is the fact that unlike many other antibiotic trials, this study was performed in a tightly controlled, very homogenous patient population all undergoing an identical operation performed by a single surgeon.

A surprising and potentially clinically important finding of this study was the marked difference in the incidence of pouchitis between the two study groups. In most series of patients undergoing ileoanal anastomosis, nonspecific enteritis or pouchitis is the most common late complication. The clinical symptoms of patients with this poorly defined and incompletely understood syndrome include high stool frequency, watery stools, fat malabsorption, urgency without defecation, nocturnal leakage, and in some cases, abdominal cramping, incontinence, and rectal bleeding. Patients also may manifest a systemic syndrome of fever, malaise, and arthralgias with features similar to those experienced by patients at the time they had active colitis.[7] The incidence of pouchitis after ileal pouch–anal anastomosis has been reported to range from 8% to 20%.[7,19,20] The etiology of this condition is unknown; however speculations have included early Crohn's disease, bacterial overgrowth, either primary or secondary malabsorption, or an immune deficiency. O'Connell et al.[22] recently reported on enteric bacteriology, absorption, morphology, and emptying in patients after ileal pouch–anal anastomosis. Twenty patients were studied a mean of 26 months after operation. Eight patients with a good result were compared to six with a poor result and six with recurrent pouchitis. Anaerobic and aerobic overgrowth of bacteria occurred in the jejunum of patients with a poor result, but not in those with a good result or with pouchitis. In contrast ileal pouch bacterial overgrowth occurred in all patients. Jejunal overgrowth of anaerobes was associated with increased stool volume. Neither pouch emptying nor histologic inflammation correated with the clinical result. Thus, in a small study population of patients with pouchitis, no distinguishing bacteriologic, morphologic, or emptying abnormalities could be found.

We reported a 17% incidence of pouchitis in our overall patient population.[7] The most striking observation from our experience has been the difference in frequency of pouchitis between patients operated on for ulcerative colitis and for familial polyposis coli. No cases of pouchitis have been observed in the latter group. This leads to speculation that pouchitis is a further manifestation of the nflammatory bowel disease. We also noted a significantly higher incidence of extracolonic systemic manifestations efore the time of surgery in those patients who develop ouchitis after ileal pouch–anal anastomosis. In our series f patients, 40% of patients with extracolonic systemic manifestations developed pouchitis, whereas only 19% of hose without extracolonic manifestations developed linical pouchitis.[23] We are uncertain as to the interpreation of the significant difference in the incidence of ouchitis between the two study populations in the current tudy. It suggests that bacterial overgrowth may play a ole in ileal pouch dysfunction; however because pouchitis ccurred at variable times after operation, even as late as 2 months, it is difficult to understand how perioperative r early postoperative antibiotics would affect the quality or quantity of flora so long after it was administered. We are now studying ileal function and dysfunction in patients following ileal pouch–anal anastomosis.

In summary the efficacy of a short perioperative course compared to an extended postoperative course of intravenous cefoxitin was assessed *via* a prospective, double-blind, randomized study in patients undergoing colectomy, mucosal proctectomy, and endorectal ileal pouch–anal anastomosis for chronic ulcerative colitis. All operations were performed in a similar fashion by a single surgeon. No intra-abdominal, pelvic, or wound infections were observed in either group. The overall and antibiotic-related complication rates were similar in both groups, although the incidence of late postoperative ileal pouchitis was significantly greater in patients who received a prolonged postoperative course of intravenous antibiotics. We conclude that despite the length of operation and the frequent episodes of frank pelvic contamination, patients undergoing ileal pouch–anal anastomosis are best managed with a standard perioperative course of prophylactic intravenous antibiotics.

## References

1. Martin LW, Fisher JE. Preservation of anorectal continence following total colectomy. Ann Surg 1982; 196:700–704.
2. Fonkalsrud EW. Endorectal ileoanal anastomosis with isoperistaltic ileal reservoir after colectomy and mucosal proctectomy. Ann Surg 1984; 199:151–157.
3. Metcalf AM, Dozois RR, Kelly KA, et al. Ileal "J" pouch-anal anastomosis: clinical outcome. Ann Surg 1985; 202:735–739.
4. Schoetz DJ Jr, Coller JA, Veidenheimer MC. Ileoanal reservoir for ulcerative colitis and familial polyposis. Arch Surg 1986; 121: 404–409.
5. Stone HH, Hooper CA, Kolb LD, et al. Antibiotic prophylaxis for gastric, biliary and colonic surgery. Ann Surg 1976; 184:443–452.
6. Cruse P. Infection surveillance identifying the problems of the high risk patient. South Med J 1977; 70(Supp 1):4.
7. Becker JM, Raymond JL. Ileal pouch-anal anastomosis: a single surgeon's experience with 100 consecutive cases. Ann Surg 1986; 204:375–383.
8. Cohen J. Statistical Power Analysis for the Behavior Sciences. New York, NY: Academic Press, 1969.
9. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet 1971; 132:323.
10. Nichols RL, Broido P, Condon RE, et al. Effect of preoperative neomycin-erthromycin intestinal preparation on the incidence of infectious complications following colon surgery. Ann Surg 1973; 178:453–462.
11. Condon RE, Barlett JG, Nichols RL, et al. Preoperative prophylactic cephalothin fails to control septic complications of colorectal operations: results of controlled clinical trial. Am J Surg 1979; 137: 68–74.
12. Evans C, Pollock AV. The reduction of surgical wound infections by prophylactic parenteral cephaloridine. A controlled clinical trial. Br J Surg 1979; 60:434.
13. Barber MS, Hirshberg BC, Rice CL, Atkins CC. Parenteral antibiotics in elective colon surgery. A prospective controlled clinical study. Surgery 1979; 286:23–28.
14. Bartlett JG, Condon RE, Gorbach SL, et al. Veterans Administration cooperative study on bowel preparation for elective colorectal

operations: impact of oral antibiotic regimen on colonic flora, wound irrigation cultures and bacteriology of septic complications. Ann Surg 1978; 188:249–254.

15. Polk HC Jr, Lopez-Mayor JF. Postoperative wound infection: a prospective study of determinant factors and prevention. Surgery 1969; 66:97–107.
16. Keighley MRB, Arabi Y, Alexander-Williams J, et al. Comparison between systemic and oral antimicrobial prophylaxis in colorectal surgery. Lancet 1979; i:894–897.
17. Kaiser AB, Herrington JL, Jacogs JK, et al. Cefoxitin versus erythromycin, neomycin, and cefazolin in colorectal operations: importance of the duration of the surgical procedure. Ann Surg 1983; 198:525–530.
18. Alexander DP, Becker JM. Cefoxitin disposition in colorectal surgery. Ann Surg 1988; 208:162–168.
19. Taylor BM, Phillips SF, Kelly KA. Altered physiology and experimental basis for reservoir. *In*: Dozois RR, ed. Alternatives to Conventional Ileostomy. Chicago: Yearbook Medical Publishers, 1985, pp 303–312.
20. Pemberton JH, Kelly KA, Beart RW Jr, et al. Ileal pouch anal anastomosis for chronic ulcerative colitis. Ann Surg 1987; 106:504–511.
21. Utsunomiya J, Iwama T. The "J" ileal pouch-anal anastomosis: the Japanese experience. *In* Dozois RR, ed. Alternatives to Conventional Ileostomy. Chicago: Yearbook Medical Publishers, 1985, pp 321–383.
22. O'Connell DR, Rankin DR, Wieland LH, Kelly KA. Enteric bacteriology, absorption, morphology and emptying after ileal pouch-anal anastomosis. Br J Surg 1986; 73:909–914.
23. Becker JM, Dunnegan DL. Ileal pouch function and dysfunction following ileal pouch-anal anastomosis. *In* MacDermott RP, ed. Inflammatory Bowel Disease: Current Status and Future Approach. Amsterdam, New York, Oxford. Excerpta Medica, 1988, pp 689–693.

# Defining the Role of Subtotal Colectomy in the Treatment of Carcinoma of the Colon

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**Seventy-two patients with colon cancer were treated by primary subtotal colectomy, including 23 patients with acute and subacute eft colon obstruction. There were two operative deaths and no cases of disabling diarrhea. One death occurred in the group with colon obstruction. Other indications for subtotal colectomy ncluded multiple polyps associated with the primary tumor (32), ynchronous carcinomas (15), a previous transverse colostomy or obstruction (8), associated severe sigmoid diverticular disease 2), age less than 50 years with a positive family history (3), adherence of the sigmoid loop to a cecal tumor (2), and metahronous carcinoma (2). There were multiple indications in several patients. Subtotal colectomy has a defined role in a wide ariety of clinical settings associated with colon cancer, including management of obstruction of the left and sigmoid colon, paricularly if the proximal colon cannot be evaluated before opration by colonoscopy or barium enema. Segmental or regional olonic resections are appropriate if the entire colon can be evalated before operation and no associated neoplasms are revealed.**

STANDARD OPERATIONS FOR the treatment of carcinoma of the colon include appropriate segmental or radical regional resections. For the treatment of obstructing carcinoma of the colon, staged procedures enerally are accepted.[1,2] For obstructing lesions of the eft colon, resection and primary anastomosis have been egarded with disfavor because of the high morbidity and mortality rates associated with this approach.[3] There are ew references to the use of subtotal colectomy (STC) in his clinical setting, most appearing in the recent literaure.[4–18]

Subtotal colectomy is the procedure of choice in the management of juvenile polyposis and synchronous colon ancers and it is generally thought to be the primary proedure when cancer of the colon is associated with synhronous adenomatous polyps in areas other than those ormally included in the scope of a regional operation.[19]

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The purpose of this paper is to review our experience with STC in the management of 72 patients with colon cancer to determine the surgical applicability and safety of the operation in a variety of clinical settings, including 23 patients presenting with acute and subacute descending colon or sigmoid colon obstruction.

On the basis of our earlier experience and that of others, it appears that STC is a useful and safe operation and that its role in the management of colonic carcinoma should be defined more clearly.[4]

## Methods and Materials

From 1973 to 1989, there were 658 cases of carcinoma of the colon at Newark Beth Israel Medical Center. Of these patients 458 were treated surgically, 72 by STC. The patients ranged in age from 26 to 89 years, with an average of 662 years. Forty-three patients were men and 29 were women. Material was collected from the tumor registry, through chart review, and personal contact with the patient or the family physician.

Surgery was performed by or under the supervision of several senior surgeons, and technical variations were few. If a portion of the sigmoid colon was preserved for distal anastomosis, the origin of the inferior mesenteric artery was preserved and the left colic artery was ligated and divided at its origin. For left-sided lesions, the inferior mesenteric vein was ligated and divided near the duodenum, thereby permitting a generous removal of mesentery and periaortic lymph node-bearing tissue, and at the same time maintaining good circulation to the distal component of the anastomosis. The iliosigmoid anastomosis was done either in end-to-end, side-to-end, or side-

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TABLE 1. *Pathology of Primary Tumors and Resected Colon*

| Condition | Number |
|---|---|
| Carcinoma | |
| Positive nodes | 22 |
| Negative nodes | 50 |
| Synchronous tumors or malignant polyp | 34 |
| Adenomatous polyps | 25 |
| Extension to pericolic SVT | 26 |
| Vilous adenoma | 7 |
| Tubular and tubulovillous adenoma | 25 |
| Diverticulosis | 12 |
| Signet ring cell carcinoma of the appendix | 1 |

Hyperplatic or mataplastic polyps not included.
SVT,

to-side fashion by hand or using a stapling device. In seven cases a preliminary transverse colostomy was performed and then a STC as a definitive procedure, resecting the colostomy and performing a primary anastomosis.

## Results

The site of the distal anastomosis was the distal sigmoid (31), the mid sigmoid (10), the proximal sigmoid (12), the rectum (14), and the distal descending colon (5).

Table 1 describes the significant pathology and the location of the primary tumors. Before operation there were 15 patients with known synchronous carcinoma and 32 with associated polyps. Postoperative pathologic examinations revealed 34 patients with synchronous carcinomas or malignant polyps and 25 with associated adenomatous polyps, 7 with villous adenomas, and 22 with tubular villous adenomas. In one case an unsuspected signet ring cell carcinoma of the appendix was found.

Table 2 lists the presenting symptoms. In 23 cases acute or subacute intestinal obstruction with associated vomiting, distention, and constipation were the major complaints.

There were two operative deaths. Table 3 lists the complications of the procedure. There were two splenic tears, one requiring splenectomy, and one minor gastroesophageal junction tear occurring during the takedown of a difficult splenic flexure. The tear was recognized and repaired without subsequent problems.

TABLE 2. *Presenting Symptoms*

| Symptom | Number |
|---|---|
| Acute large bowel obstruction | 23 |
| Anemia, rectal bleeding | 31 |
| Cramps and pain | 20 |
| Constipation | 16 |
| Anorexia | 7 |
| Diarrhea | 6 |
| Weight loss | 6 |
| Mass | 2 |
| Occult blood in stool | 2 |
| Prior history of cancer and polyps | 2 |

TABLE 3. *Postoperative Complications*

| Complication | Number |
|---|---|
| Atelectasis | 5 |
| Ileus | 5 |
| Splenic injury | 2 |
| Esophogealgastric junction tear | 1 |
| Pelvic abscess | 1 |
| Intestinal obstruction | 1 |
| Wound infection | 2 |
| Diarrhea | 3 |
| Congestive heart failure | 1 |

The average duration of hospitalization in the group of patients was 20.9 days from admission to discharge; one secondary admission and operation was required for intestinal obstruction secondary to a pelvic abscess. That patient subsequently died.

Table 4 describes the current bowel habits of the group surveyed. Fifty patients had less than five bowel movements per day and only eight patients had more than five. Information was not available on 13 patients. No patient was disabled by diarrhea. The site of the distal anastomosis has less relationship to the frequency of bowel movements than does the amount of retained terminal ileum. In five of the eight patients having more than five bowel movements per day, more than 10 cm of terminal ileum was included in the specimen. In those patients with fewer than three bowel movements a day (32), only three of the resected bowel specimens contained more than 10 cm of ileum.

Virtually all of the patients in this series had Dukes B or C lesions. There were 18 late deaths, 16 due to metastatic cancer, 1 due to a cerebrovascular accident, and 1 due to an acute myocardial infarction. Ten patients received chemotherapy for treatment of metastatic disease and seven patients received chemotherapy in an adjuvant therapy protocol and are free of disease. One patient developed a rectal carcinoma 5 years after STC for obstructing colon cancer associated with multiple polyps and synchronous colon carcinomas. He underwent an abdominoperineal resection and terminal ileostomy.

TABLE 4. *Bowel Habits More than 60 Days After Operation*

| Number of Bowel Movements | Number of Patients |
|---|---|
| 1–3 | 35 |
| 3–5 | 16 |
| 5+ | 8 |
| Constipated | 3 |

No patients were incapacitated by diarrhea.

## Discussion

In a previous publication, an argument for the increased use of subtotal colectomy in the management of colonic carcinoma was presented.[4] Thirty-one additional STCs have increased our experience to 72 cases. Subtotal colectomy continues to be a useful operation in a variety of clinical settings.

Table 5 presents the reason for choosing STC as preference for segmental or traditional regional resections. In one third of the cases there was more than one reason for selecting this procedure.

There is no doubt that the presence of known synchronous carcinomas in separate segments of the colon constitutes a clear indication for STC as the procedure of choice. The combination of a primary malignant tumor and multiple scattered polyps also is a strong indication.

It is important to note that many sigmoid and descending colon carcinomas present with varying degrees of retrograde obstruction to the passage of barium and colonoscope. Therefore proper preoperative evaluation of the proximal colon and appropriate planning for the extent of resection of the colon are not possible. Even careful palpation of the proximal colon in these cases, and certainly in those with acute obstruction, will be inaccurate. In this setting STC will prevent the surgeon from missing significant lesions in the proximal segments of colon. In fact unsuspected synchronous carcinomas and malignant polyps were found in 17 cases in this series. It may be that patients with retrograde obstruction constitute a good group to perform primary STC rather than staged procedures. Massive proximal distention and severe electrolyte imbalance are not always present so that some of these patients are satisfactory candidates for a one-stage procedure. Although synchronous carcinomas are said to occur in only 2% to 4% of cases, frequent finding of proximal lesions in this series suggests that the true incidence of synchronous neoplasms may be much higher. Indeed several authors report the presence of synchronous neoplasms in more than 50% of the patients with obstructive tumors of the colon.[19-25]

It appears that one-stage STC with ileosigmoid anastomosis can be done safely in almost any clinical setting.

TABLE 5. *Indications for STC**

| Indication | Number |
|---|---|
| Associated polyps | 32 |
| Acute or subacute colonic obstruction | 23 |
| Known synchronous carcinoma | 15 |
| Associated sigmoid diverticulosis | 7 |
| Prior transverse colostomy for obstruction | 8 |
| Young patient (<50 years old) with positive family history | 3 |
| Adherence of sigmoid colon to cecal tumor | 2 |
| Metachronous carcinoma | 2 |

* Several patients had multiple indications.

TABLE 6. *Subtotal Colectomy for Obstructing Carcinoma of the Left and Sigmoid Colon*

| Author | Year | No. Cases | Deaths |
|---|---|---|---|
| Hughes[8] | 1970 | 17 | 0 |
| Valerio[15] | 1978 | 5 | 0 |
| Klatt[9] | 1981 | 5 | 0 |
| Terry[16] | 1981 | 5 | 1 |
| Deutsch[6] | 1983 | 14 | 1 |
| Glass[7] | 1983 | 7 | 1 |
| Weddel* | 1983 | 12 | 1 |
| Adloff[17] | 1984 | 13 | 1 |
| Morgan[10] | 1985 | 16 | 2 |
| Samama[11] | 1986 | 3 | 0 |
| Alves-Pereira[18] | 1989 | 17 | 1 |
| Halevy[13] | 1989 | 22 | 1 |
| Brief* | 1989 | 23 | 1 |

* No reference given.

Although groups of patients are not comparable, operative mortality rates for STC in our series and others remain much lower than those reported for staged procedures.[4-18] Morbidity rates for primary resections are quite high and thus the procedure is not recommended.[3] Our own results for STC in the obstructing lesions as well as those of others (Table 6) continue to be good enough to justify its use in selected cases. Our indications are the absence of electrolyte imbalance, sufficient work-up time to restore hydration and blood volume, a distal colon free of lesions to the site of obstruction, and the absence of massive small and large bowel distention. In this setting the obstructed unprepared large bowel is removed with the tumor. Others have called this an extended right hemicolectomy.[14] Since our publication in 1983, several authors have confirmed the validity and safety of this approach to the clinical problem of left-sided colonic obstruction. An ileocolic anastomosis is safer than a colocolic anastomosis. Suture line recurrences are rare when compared to colocolic anastomosis and technical complications and leakage occur infrequently.[27] Table 7 summarizes these results. In almost any setting tension on the suture line must be avoided. A good blood supply should never be a problem on the small bowel side of the anastomosis. A variety of techniques can be used for the anas-

TABLE 7. *Suture Line Recurrences in Two Types of Anastomoses (Wright et al.[26])*

| Types of Anastomoses | No. Patients | No. Recurrences | Recurrence Rate (%) |
|---|---|---|---|
| Proximal ileocolic | 272 | 2 | 0.7 |
| Proximal colocolic | 131 | 20 | 15.3 |
| Distal colocolic | 435 | 49 | 11.3 |
| Distal ileocolic* | 72 | 0 | 0 |

* Newark Beth Israel Medical Center experience.

tomosis, including end-to-end, side-to-end, and functional end-to-end with a lateral stapled anastomosis. In most cases the anastomosis can be done without wound contamination.

The functional results of STC are satisfactory. If an adequate amount of terminal ileum is retained, bile salt resorption is normal and diarrhea avoided. Even if the anastomosis extends to the upper rectum, adaptive changes occur and bowel function is satisfactory (Table 4).[28]

In seven cases the acute obstruction was severe enough to require transverse colostomy; in one case a cecostomy was performed. After the patient's condition improved, the proximal bowel in the right and left sides of the colon proximal to the obstruction were studied colonoscopically. In this group additional colonic lesions suggested that a STC and colostomy resection be done as a second stage operation, thereby eliminating a three-stage procedure. There was one death 30 days after operation from a pelvic abscess and intestinal obstruction.

In seven cases severe diverticulitis of the descending and sigmoid colon associated with an ascending colon carcinoma dictated that a STC be performed, with an ileosigmoid anastomosis beyond the diverticulitis. Failure to resect the involved colon may aggravate the diverticulitis and complicate management.

In two cases the development of metachronous carcinoma in the left colon following a previous right colectomy dictated the performance of the STC at the time of the second resection.

In two cases adherence of the sigmoid loop to a cecal carcinoma necessitated STC so that an *en bloc* resection could be carried out in one stage.

In three cases the young age of the patient and a positive family history, combined with the favorable nature of the tumor, suggested STC as the primary procedure. Obviously this is a relative indication because metachronous carcinoma of such patients is rare (2% to 3%). Few of these patients, however, have been followed for more than 10 years, and the incidence of metachronous carcinoma at 20 or 30 years might be expected to be higher. Adequate data in this area is lacking.

In one case rectal carcinoma developed 5 years after STC, requiring abdominal–perineal resection and an end ileostomy.

After STC regular examinations of the distal colon and rectum are important in detecting and dealing with new neoplasms. Flexible sigmoidoscopy is performed easily after STC and is better than barium enemas for follow-up examination.

Contraindications to STC are relatively few. The operation should not be preferred in poor-risk patients or those with incurable disease. If a patient has a right-sided tumor and the left colon is clear of disease, or has a left colon cancer with no lesions proximal to the tumor, a regional resection is appropriate.

## Conclusions

Subtotal colectomy is the operation of choice in the management of colonic carcinoma associated with synchronous carcinoma or multiple polyps. There are a wide variety of clinical settings in which it may be used, including acute or subacute obstructing lesions of the left or sigmoid colon, particularly if the proximal colon cannot be evaluated before operation by colonoscopy or barium enema.

Subtotal colectomy should not be used as a primary operation if the patient is an extremely poor risk or has massive proximal distention of the bowel. Criteria for selection of patients for STC with acute obstruction need to be better defined.

Morbidity and mortality rates for STC are low and the procedure has important clinical benefits. It should be considered a primary procedure for young patients. Long-term survival after STC is not different from segmental or standard regional operations. In all instances survival is a function of the stage of the tumor.

Segmental or regional colonic resections are appropriate procedures when the entire bowel can be fully evaluated before operation and the studies reveal no associated tumors.

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## References

1. Carson S. Carcinoma obstructing the left side of the colon. Arch Surg 1977; 112:523–526.
2. Clark J, Hall A, Mossa AR. Treatment of obstructing cancer of the colon and rectum. Surg Gynecol Obstet 1975; 141:541–544.
3. Irvin T. The treatment of colonic cancer presenting with intestinal obstruction. Br J Surg 1977; 64:741–744.
4. Brief DK, Brener BJ, Goldenkranz R, et al. An argument for increased use of subtotal colectomy in the management of carcinoma of the colon. Am Surg 1983; 49(2):66–72.
5. Loff M, Arnold JP, Ollier JC, et al. Urgent subtotal colectomy in the treatment of obstructing cancers of the left colon. A reasonable approach to therapy or not? Chirurgie 1984; 110:167–171.
6. Deutsh AA, Zelikovsky A, Sternberg A, Reiss R. One-stage subtotal colectomy with anastomosis for obstructing carcinoma of the left colon. Dis Colon Rectum 1983; 26:227–230.
7. Glass RL, Smith LE, Cochran RC. Subtotal colectomy for obstructing carcinoma of the left colon. Am J Surg 1983; 145:335–336.
8. Hughes ESR, McDermott FT, Pulgase AL, Nottle P. Total and subtotal colectomy for colonic obstruction. Dis Colon Rectum 1985; 28:162–163.
9. Klatt GR, Martin WH, Gillespie JT. Subtotal colectomy with primary anastomosis without diversion in the treatment to obstructing carcinoma of the left colon. Am J Surg 1981; 141:577–578.
10. Morgan WP, Jenkins N, Lewis P, Aubrey DA. Management of obstructing carcinoma of the left colon by extended right hemicolectomy. Am J Surg 1985; 149:327–329.

11. Samama G, Buford JL, Girard A. Cancer of the left colon revealed by obstruction: treatment by subtotal colectomy and immediate ileosigmoid anastomosis. Presse Med 1986; 15:2070–2071.
12. Wilson RG, Gollock JM. Obstructing carcinoma of the left colon managed by subtotal colectomy. J R Coll Surg Edinb 1989; 34: 25–56.
13. Halevy A, Levi J, Orda R. Emergency subtotal collectomy: a new trend for treatment of obstructing carcinoma of the left colon. Ann Surg 1989; 210:220–223.
14. Hughes ESR. Subtotal colectomy for carcinoma of the colon. Proc R Soc Med 1970; 63(Suppl):41–42.
15. Valerio D, James PJ. Immediate resection in the treatment of large bowel emergencies. Br J Surg 1978; 65:712–716.
6. Terry BG, Bearth RW. Emergency abdominal colectomy with primary anastomosis. Dis Colon Rectum 1981; 23:1–4.
7. Adloff M, Arnaud JP, Ollier JC. Emergency subtotal colectomy in the treatment of obstructive cancer of the left colon. An audacious or rational attitude? Chirugie 1984; 110(2):167–171.
8. Alves-Pereira C. La colectomie subtotale d'urgence dans les obstructions par cancer du colon gauche. Minerva Chir 1989; 44:245–248.
9. Teicher I, Abrahams JF. The treatment of selected cases of multiple polyps, familial polyposis and diverticular disease of the colon by subtotal colectomy and ilioproctostomy. Surg Gynecol Obstet 1956; 103:136–146.
20. Moertel CG, Bargen JA, Dockerty MD. Multiple carcinomas of the large intestine: a review of the literature and a study of 261 cases. Gastroenterology 1958; 34:85–98.
21. Anderson M. Synchronous cancer of the colon: a case for more definitive resection in colon cancer. J Natl Med Assoc 1978; 70: 8.
22. Heald RJ, Bussey HG. Clinical experiences at St. Martins Hospital with multiple synchronous cancer of the colon and rectum. Dis Colon Rectum 1975; 18:6.
23. Davita V, Hillmons S, Rosenberg S. Colorectal cancer. Principles and Practices of Oncology. Philadelphia: JB Lippincott, 1982, pp 707–708.
24. Bat L, Neumann G, Shemesh E. The association of synchronous neoplasms with occluding colorectal cancer. Dis Colon Rectum 1985; 28:149–151.
25. Chu DZJ, Giacco G, Mardia RG Guinee VF. The significance of synchronous carcinoma and polyps in the colon and rectum. Cancer 1986; 57:445–450.
26. Wright HK, Thomas WH, Cleveland JC. The low recurrence rate of colonic carcinoma in ileo colic anastomosis. Surg Gynecol Obstet 1969; 129:960.
27. Fielding L. Anastomotic integrity after operations for large bowel cancer. Br Med J 1980; 281:411.
28. Lillehei RC, Wangenstein OH. Bowel function after colectomy for cancer, polyps and diverticulitis. J Am Med Assoc 1955; 159: 193.

# The Peritoneal Environment During Infection

## *The Effect of Monomicrobial and Polymicrobial Bacteria on $pO_2$ and pH*

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**Intraperitoneal (IP) abscesses frequently are composed of aerobes and anaerobes, and, in experimental models, a particulate adjuvant. The environmental changes effected by these components, either singularly or in combination, have not been well defined. The IP $pO_2$, pH, and recoverable bacteria from the peritoneum of rats were quantified over 6 hours during simple aerobic and anaerobic infections and during mixed peritonitis with and without a sterile feces–barium sulfate adjuvant (SFA). Fourteen groups were studied, receiving intraperitoneally, at time of oxygen probe placement, 1 mL normal saline (control), *Escherichia coli* (EC), *Bacteroides fragilis* (BF), SFA alone, or a mixture of EC and BF, EC and SFA, BF and SFA, or EC, BF, and SFA. Control animals exhibited a stable IP $pO_2$ and pH during 6 hours. In monomicrobial EC peritonitis, inocula well below the $LD_{50}$ produced an increased IP $pO_2$ and reduced arterial–peritoneal gradient (APG), with a stable IP pH. By 6 hours lethal doses of EC produced a dramatic decline in IP $pO_2$, with no change in arterial $pO_2$ as well as acidic IP and arterial pHs. Simple BF peritonitis caused no or minor elevations in IP and arterial $pO_2$ with no change in pH. During mixed infections a significant decline in the IP $pO_2$ and pH at 6 hours in those groups infected with both SFA and EC of a moderate, normally sublethal inoculation was observed, while arterial $pO_2$ was unchanged and arterial pH was decreased only slightly. Concomitantly there was a significantly increased number of aerobic bacteria in those groups with SFA as adjuvant compared to similar inocula without SFA. This study demonstrates the complex interactions of bacteria, sterile particulate adjuvant (SFA), and the host peritoneum. It suggests that the combination of SFA and aerobic bacteria alter the peritoneal environment to one permitting anaerobic growth and promoting abscess formation.**

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CLINICAL INTRAPERITONEAL (IP) INFECTIONS usually are polymicrobial, as they are comprised of both aerobic and anaerobic organisms.[1–4] Experimental models also have demonstrated a synergy between these two components,[5] and, in most cases, the necessity for anaerobes for consistent abscess formation.[6,7] Nonbacterial adjuvant have frequently been added as well to promote abscess formation while avoiding the lethality of higher bacterial inocula. Weinstein et al.[8] developed an early rat model of mixed peritonitis leading to IP abscess formation that relied on the presence of barium sulfate as a local irritant and two gelatin capsules to assure localization. Others have shown that other forms of inanimate material, including fibrin,[9] bran,[10] or agar,[11] can be used as well. The pathogenesis of this synergy between aerobes, anaerobes, and particulate matter is unclear. It has been proposed that the ability to effect abscesses by aerobes and anaerobes may be the consequence of alterations in the peritoneal environment resulting from the metabolism and by-products of the bacteria.[12] The nature of these environmental changes, however, has not been well characterized thus far.

In the only previous attempt at the direct measurement of IP $pO_2$ and $pCO_2$ during peritonitis, Renvall and Niinkoski[13] noted a steady decrease in $pO_2$ and increase in $pCO_2$ during 24 hours in animals during intra-abdominal infection. These experiments were hampered, however, in that the induction of peritonitis was by a poorly controlled transanal traumatic rupture of the colon. Close to 30% of their animals did not develop acute peritonitis and quantification of the bacterial inoculum was, of course, impossible. The effect of the different components of peritonitis on the peritoneal environment, therefore, remains unspecified.

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This study was designed to examine the early changes in peritoneal environment, specifically $pO_2$ and pH, and bacterial growth using a rat model of peritonitis. We first studied the effects of monomicrobial *Escherichia coli* and *Bacteroides fragilis* infections on sterile feces–barium sulfate suspension, which further allowed the assessment of these parameters in conditions known to be favorable for the formation of abscesses.

## Materials and Methods

### *Animal Preparation*

All experiments were performed in 350 to 400 g male Sprague-Dawley rats (Hilltop Laboratories, Scottdale, PA) housed in cages and fed Purina rat chow® (St. Louis, MO) and water *ad libitum*. Tonometers were constructed by inserting 22-gauge intravenous (IV) catheters, trimmed to 1 cm in length, into 5-cm segments of Silastic® tubing (internal diameter = 0.3 inches, external diameter = 0.65 inches; Dow-Corning, Midland, MI) selected for its documented gas permeability.[14] General anesthesia was induced in rats using a 5% halothane/air mixture and maintained with 1.25% halothane. The abdomen was prepped with 70% isopropyl alcohol, and, using sterile technique, was opened with a 2-cm midline incision. A puncture wound was created in the left flank using a large-gauge needle, and the tonometer was introduced through the abdominal wall into the peritoneal cavity with the catheter hub remaining outside. A second puncture wound was made in the left lower quadrant and the tonometer end without the IV catheter was brought out through this to project 0.5 cm from the skin. Both tonometer ends were secured to the rats skin using 4-0 silk (Fig. 1). Intraperitoneal pH was measured, 1 mL of normal saline and the appropriate infecting material, depending on the group (Table 1), was placed into all quadrants, and the abdominal wall and skin were closed using a single running 3-0 nylon suture. Tail arterial blood was obtained and rats were allowed to awaken.

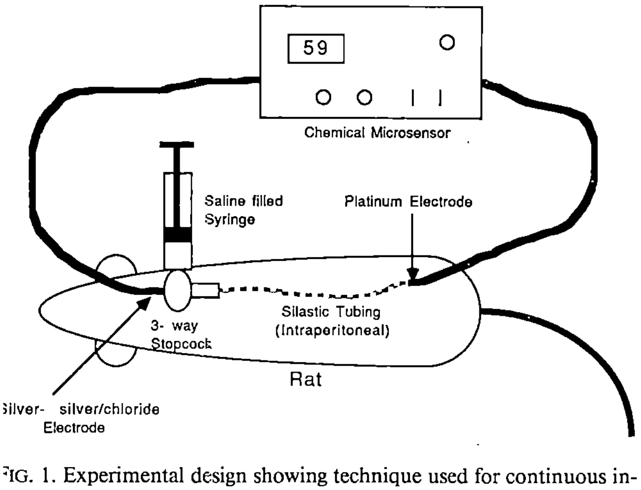


FIG. 1. Experimental design showing technique used for continuous intraperitoneal $pO_2$ monitoring.

TABLE 1. *Experimental Design as Number of Animals and Composition of Intraperitoneal Inocula Injected by Group*

| Group | Animals Inoculated | Log CFU *E. coli* Inoculated | Log CFU *B. fragilis* Inoculated | Ml Sterile Stool-Barium Sulfate Inoculated |
|---|---|---|---|---|
| 1 | 7 | 0 | 0 | 0 |
| 2 | 6 | 5 | 0 | 0 |
| 3 | 5 | 8 | 0 | 0 |
| 4 | 6 | 9 | 0 | 0 |
| 5 | 5 | 10 | 0 | 0 |
| 6 | 4 | 0 | 6 | 0 |
| 7 | 4 | 0 | 8 | 0 |
| 8 | 6 | 0 | 9 | 0 |
| 9 | 5 | 0 | 10 | 0 |
| 10 | 5 | 8 | 9 | 0 |
| 11 | 4 | 0 | 0 | 1 |
| 12 | 5 | 8 | 0 | 1 |
| 13 | 5 | 0 | 9 | 1 |
| 14 | 6 | 8 | 9 | 1 |

### *$PO_2$ and pH Measurements*

Intraperitoneal pH was measured at the time of tonometer placement and just before the animals were killed using a standard pH probe (American Scientific [McGaw Park, IL] H3725-103) and an Orion (Boston, MA) SA 720 pH meter. Rats were anesthetized hourly for 10 minutes with halothane for purposes of IP $pO_2$ measurement and blood drawing and were allowed to awaken between measurements until they were killed at 6 hours. As described by Gottrup et al.,[15] the Silastic® tubing was filled with normal saline at 37 C and a silver–silver chloride electrode placed through a three-way stopcock with a saline-filled syringe in the third port was attached to the IV catheter hub; a sheathed, open-ended platinum electrode was placed in the opposite end. Changes in electric potential and, therefore, IP $pO_2$ were assessed after stabilization (10 minutes) with a Transidyne General (now Diamond General) Chemical Microsensor 1201 with an electrode potential of −0.680 volts and calibrated with the $pO_2$ of normal saline at 37 C, as measured with a Dow-Corning 158 blood gas machine. Arterial blood was obtained percutaneously from the tail artery and pH, $pO_2$, and $pCO_2$ were determined with the blood gas machine.

### *Bacteria*

*Escherichia coli* was grown from a single colony off a stock plate of a clinical isolate (obtained from G. T. Rodeheaver, University of Virginia) by incubating in brain-heart infusion (BHI) broth for 18 hours in a 37 C oscillating water bath. Cultures were centrifuged for 12 minutes at 2400 rpm at 4 C and pellets were further washed twice in 0.9% normal saline. After the second wash, bacteria were quantified using serial dilutions and plate enumerations, and concentrations were adjusted as necessary. *Bacteroides fragilis* (ATCC #23745) was prepared by inoculating 1 mL of a stock chopped meat broth solution into supplemented BHI broth and incubated for 18 hours at 37 C. Cultures were centrifuged for 12 minutes at 2400 rpm and pellets were further washed twice in prereduced Hanks' balanced salt solution. After washing bacteria were diluted serially and quantified in a Coy anaerobe chamber (Coy Manufacturing, Ann Arbor, MI), and concentrations were adjusted as needed.

Sterile feces–barium sulfate suspension was prepared by mixing dried, weighed rat stool with an equal weight of BHI broth, straining through coarse mesh gauze, and mixing in a 1:1 volume:volume ratio with a 10% weight: volume barium sulfate suspension. The suspension was sterilized in a steam autoclave for 15 minutes at 121 C.

Quantitative peritoneal cultures were performed as previously described.[16] Briefly, 10 mL of anaerobic dilution solution was injected into the peritoneum after the animals were killed, animals were agitated for 60 seconds, and lavage fluid was removed after laparotomy, serially diluted, and plated quantitatively both aerobically and anaerobically. Colony-forming units were counted after 48 hours of incubation and total intraperitoneal bacterial counts were calculated.

### *Statistics*

Statistical analysis was performed using unpaired, two-tailed Student's T test with the aid of a MacIntosh Plus® computer and StatWorks® software package (Cricket-Software, Philadelphia, PA).

TABLE 2. *Intraperitoneal pH at Time of Tonometer Implantation and Killing by Group*

| Group and Inoculum | Intraperitoneal pH (±SEM) at Time of Tonometer Placement | Intraperitoneal pH (±SEM) at Time of Killing |
|---|---|---|
| 1. Saline | 7.40 ± 0.01 | 7.40 ± 0.02 |
| 2. $10^5$ EC | 7.39 ± 0.02 | 7.40 ± 0.01 |
| 3. $10^8$ EC | 7.40 ± 0.02 | 7.38 ± 0.02 |
| 4. $10^9$ EC | 7.41 ± 0.02 | 7.40 ± 0.07 |
| 5. $10^{10}$ EC | 7.40 ± 0.03 | 6.60 ± 0.15* |
| 6. $10^6$ BF | 7.38 ± 0.05 | 7.42 ± 0.01 |
| 7. $10^8$ BF | 7.39 ± 0.02 | 7.40 ± 0.02 |
| 8. $10^9$ BF | 7.40 ± 0.01 | 7.42 ± 0.03 |
| 9. $10^{10}$ BF | 7.41 ± 0.01 | 7.47 ± 0.02* |
| 10. $10^8$ EC + $10^9$ BF | 7.39 ± 0.02 | 7.42 ± 0.01 |
| 11. 1 ml SFA | 7.40 ± 0.02 | 7.41 ± 0.01 |
| 12. $10^8$ EC + 1 mL SFA | 7.41 ± 0.02 | 7.23 ± 0.02* |
| 13. $10^9$ BF + 1 mL SFA | 7.42 ± 0.03 | 7.39 ± 0.01 |
| 14. $10^8$ EC + $10^9$ BF + 1 mL SFA | 7.40 ± 0.01 | 7.15 ± 0.02* |

All figures are ±SEM.
* $p < 0.01$ *vs.* control by Student's t test.

## Results

### *Controls (Group 1)*

Mean intraperitoneal $pO_2$ at catheter implantation in controls was 50 ± 0.92 mmHg, and remained stable between 53 and 58 mmHg throughout the study period (Fig. 2). Intraperitoneal pH was 7.40 ± 0.01 (SEM) in controls at time of laparotomy and remained neutral at 6 hours (Table 2). Initial arterial $pO_2$ was 74 ± 4.3 mmHg, and was noted to be stable through the course of the experiment with a slight but consistent decline at 6 hours, to 62 ± 1.2 mmHg (Fig. 3). At time of tonometer implantation,

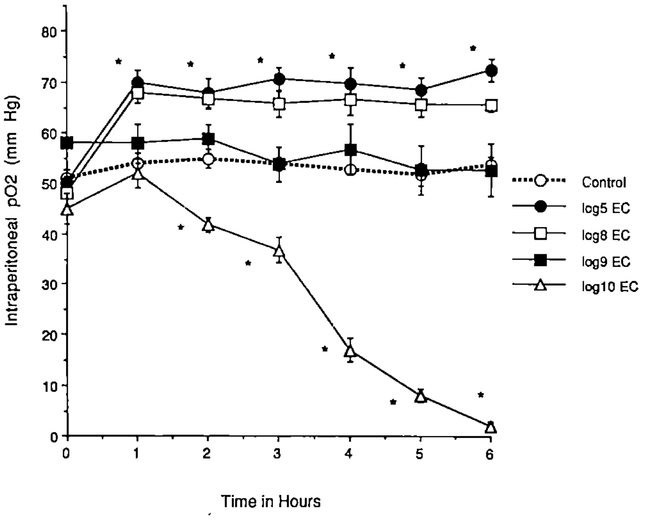


FIG. 2. Effect of different inocula of *Escherichia coli* (EC) on intraperitoneal $pO_2$. *Indicates $p \le 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

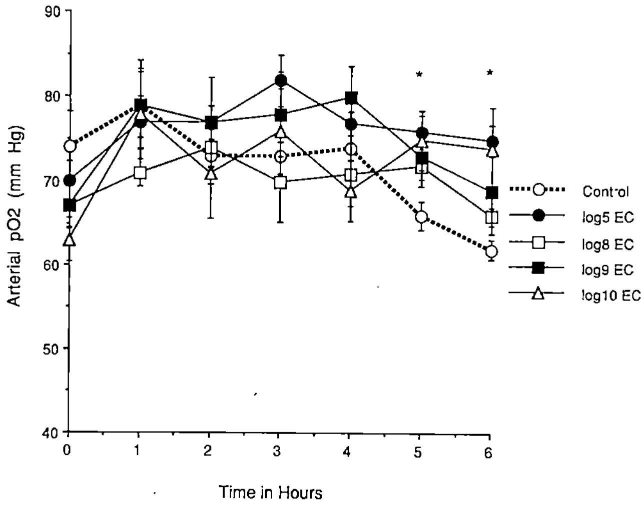


FIG. 3. Effect of different inocula of *Escherichia coli* (EC) on arterial $pO_2$. *Indicates $p \le 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

arterial pH was 7.38 ± 0.02 and remained neutral, with a final 6-hour value of 7.44 ± 0.02 (Fig. 4). Recovery of peritoneal bacteria from controls was limited to one case of of contamination with approximately 300 gram-positive cocci. Otherwise the peritoneum were noted to be sterile to the limits of detectability (Table 3).

### E. coli *Peritonitis (Groups 2 to 5)*

In *E. coli* peritonitis, changes in the intraperitoneal $pO_2$ were highly inoculum dependent. At inocula well below the $LD_{50}$, $10^5$ and $10^8$ colony-forming units (cfu), intraperitoneal $pO_2$ increased significantly ($p < 0.01$ by unpaired Student's T test *versus* controls) by 1 hour and remained elevated through the ensuing 6 hours. With an inoculum of $10^9$ cfu (approximate $LD_{50}$), the intraperitoneal $pO_2$ decreased back to that found in controls. With $10^{10}$ cfu, a lethal inoculum, intraperitoneal $pO_2$ was unchanged early, but by 3 hours had decreased significantly ($p < 0.01$) below controls, and by 6 hours had decreased to a mean of 6 ± 1 mmHg (Fig. 2). Frequently death ensued shortly thereafter. At time of tonometer implantation, intraperitoneal pH was neutral in all groups and was not different ($p > 0.1$) when the animals were killed in all but the animals receiving $10_{10}$ *E. coli,* where the intraperitoneal pH at 6 hours was 6.60 ± 0.15, significantly ($p < 0.01$) less than control (Table 2). The arterial $pO_2$ in the infected groups was similar to controls ($p > 0.1$) at time zero and sustained stable values through the time that the animals were killed; due to the decline in control arterial $pO_2$ at 5 and 6 hours, however, arterial $pO_2$ was slightly greater than controls in most groups (Fig. 3). From 0 to 2 hours, arterial pH was not significantly different from controls ($p > 0.1$). In the groups with the two lowest inocula, arterial pH remained neutral throughout the study period. With $10^9$ cfu, however, arterial pH became mildly but significantly ($p < 0.05$) less than controls at 3 hours and remained that way through 6 hours, with the exception of the 5-hour time period; the final pH value was 7.36 ± 0.02. In animals receiving $10^{10}$ *E. coli,* the arterial pH became and remained significantly ($p < 0.01$) lower at 3 hours and declined thereafter, reaching a low of 7.16 ± 0.03 at 6 hours (Fig. 4). As would be expected, the number of *E. coli* recovered when the animals were killed was proportional to the inoculum. Roughly one log fewer bacteria were recovered than implanted; the notable exception was those animals receiving $10^{10}$ *E. coli,* where $10^{10}$ cfu were recovered as well (Table 3).

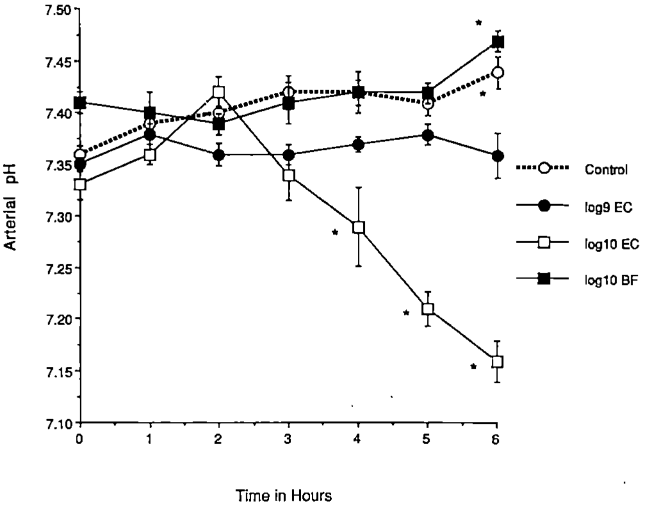


FIG. 4. Effect of selected monomicrobial *Escherichia coli* (EC) or *Bacteroides fragilis* (BF) inocula on arterial pH. *Indicates $p \leq 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

TABLE 3. *Intraperitoneal Bacteria Recovered at Time of Killing in Groups with Monomicrobial Peritonitis*

| Group and Inoculum | Log CFU *E. coli* Recovered | Log CFU *B. fragilis* Recovered |
|---|---|---|
| 1. Saline | ≤2 | ≤2 |
| 2. $10^5$ *E. coli* | 4.0 ± 0.3 | ≤2 |
| 3. $10^8$ *E. coli* | 7.3 ± 0.8 | ≤2 |
| 4. $10^9$ *E. coli* | 7.7 ± 0.2 | ≤2 |
| 5. $10^{10}$ *E. coli* | 10 ± 1.1 | ≤2 |
| 6. $10^6$ *B. fragilis* | ≤2 | 4.9 ± 0.4 |
| 7. $10^8$ *B. fragilis* | ≤2 | 7.4 ± 0.8 |
| 8. $10^9$ *B. fragilis* | ≤2 | 8.3 ± 0.2 |
| 9. $10^{10}$ *B. fragilis* | ≤2 | 9.3 ± 0.2 |

### B. Fragilis *Peritonitis (Groups 6 to 9)*

With simple *B. fragilis* peritonitis, intraperitoneal $pO_2$ at time zero was similar to controls. Over time and through the time that the animals were killed, a very low inoculum, $10^6$ cfu, produced no effect on intraperitoneal $pO_2$, while higher inocula of $10^8$, $10^9$, or $10^{10}$ organisms caused a significant ($p < 0.01$ *versus* controls) increase by 1 hour that was sustained through 6 hours (Fig. 5). Intraperitoneal pH was neutral at the time of laparotomy in all groups and was neutral when animals were killed in all except those animals receiving $10^{10}$ *B. fragilis,* where final intraperitoneal pH was 7.47 ± 0.02, significantly greater ($p < 0.01$) than controls (Table 2). Arterial $pO_2$ was similar to controls ($p > 0.1$) at time zero, and, with the exception of animals receiving $10^{10}$ cfu, remained stable through time of killing. Again, due to the decline in control arterial $pO_2$ at 5 and 6 hours, arterial $pO_2$ was usually slightly, but significantly, greater than controls at these times. In animals receiving $10^{10}$ organisms, arterial $pO_2$ peaked at 1 hour at 101 ± 6.6 mmHg, then declined to a stable 89 ± 5.1 mmHg, with a 6-hour value of 87 ± 5.0 mmHg. At all times this value was significantly greater than controls (Fig. 6). Through 5 hours arterial pH was not significantly different ($p > 0.1$) from controls in the experimental groups. In animals inoculated with $10^{10}$ *B. fragilis,*

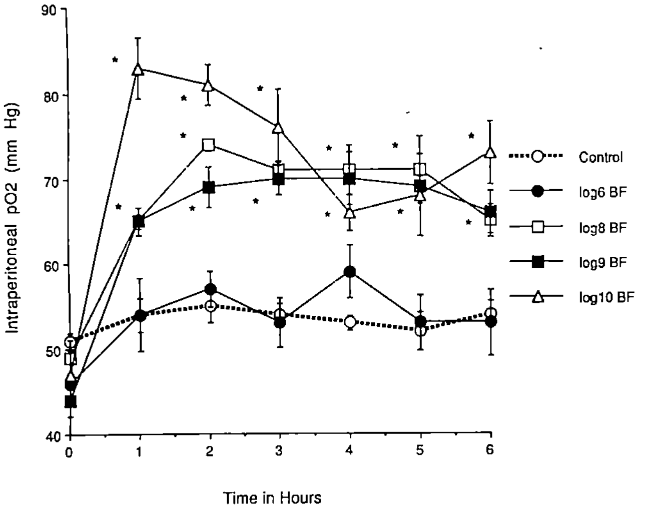


FIG. 5. Effect of different inocula of *Bacteroides fragilis* (BF) on intraperitoneal $pO_2$. *Indicates $p \leq 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

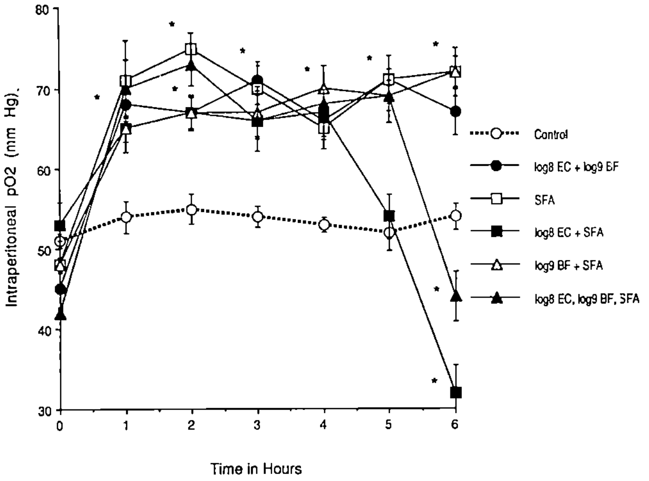


FIG. 7. Effect of mixed *Escherichia coli* (EC) and *Bacteroides fragilis* (BF) or sterile feces adjuvant (SFA) inocula on intraperitoneal $pO_2$. *Indicates $p \leq 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

the arterial pH exhibited a significant ($p < 0.01$) increase to 7.47 ± 0.02 at 6 hours only (Fig. 4). In all groups the number of *B. fragilis* recovered at time of killing was about one log fewer than the inoculum (Table 3). There were no deaths in any *B. fragilis* group.

### *Mixed* E. coli–B. fragilis *Peritonitis Without SFA (Group 10)*

At laparotomy there was no difference in intraperitoneal $pO_2$ between control and an inoculum of $10^8$ *E. coli* plus $10^9$ *B. fragilis*. By 1 hour intraperitoneal $pO_2$ was significantly greater than controls ($p < 0.01$) and remained so through 6 hours (Fig. 7). This increase was similar to that seen with either element of the inoculum alone. Intraperitoneal pH started at 7.40 ± 0.01 and remained neutral at the time animals were killed (Table 2). Arterial $pO_2$ was not different from controls until hours 5 and 6, when the experimental group maintained a steady value of 75 mmHg, but controls declined slightly to a significantly lower value (Fig. 8). Arterial pH was neutral throughout the study and at no times different from control (Fig. 9). When animals were killed, a mean of $2.1 \times 10^7$ *E. coli* and $3.1 \times 10^8$ *B. fragilis* were cultured from the peritoneum, with neither significantly different from when either component was inoculated separately (Fig. 10).

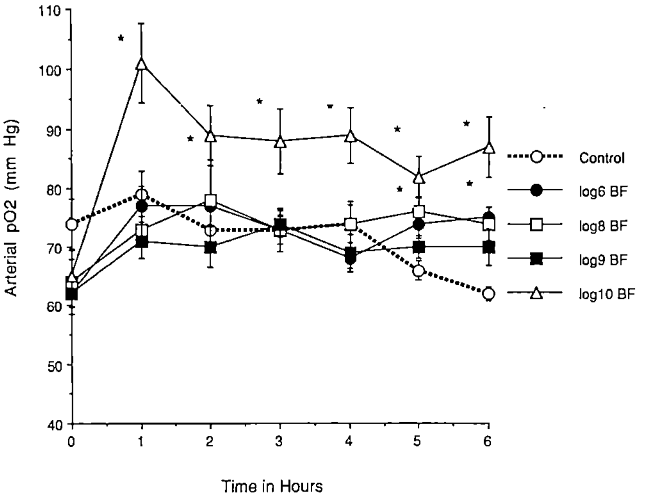


FIG. 6. Effect of different inocula of *Bacteroides fragilis* (BF) on arterial $pO_2$. *Indicates $p \leq 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

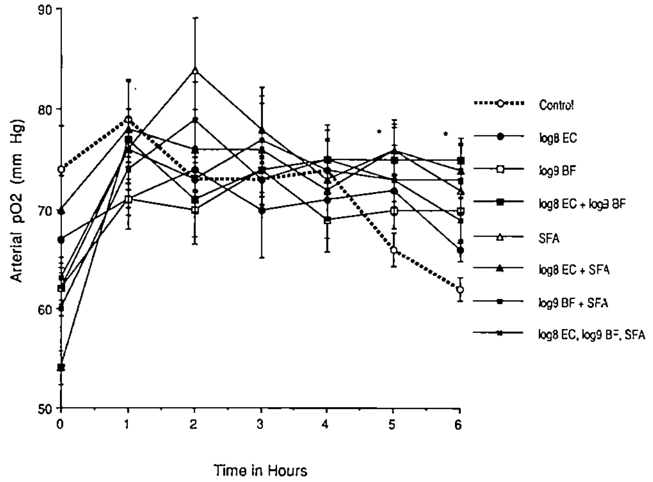


FIG. 8. Effect of mixed *Escherichia coli* (EC) and *Bacteroides fragilis* (BF) or sterile feces adjuvant (SFA) inocula on arterial $pO_2$. *Indicates $p \leq 0.05$ *versus* uninfected controls; error bars indicate standard error of the mean.

### *Sterile Feces–Barium Sulfate Adjuvant Enhanced Peritonitis (Groups 11 to 14)*

Again there were no differences in intraperitoneal $pO_2$ between controls and any group at time zero. By 1 hour after tonometer implantation, all treated groups had significantly increased intraperitoneal $pO_2$ ($p < 0.01$ by Student's T test). In groups receiving the adjuvant alone or with $10^9$ *B. fragilis*, this elevation persisted throughout the 6-hour study period. In rats infected with $10^8$ *E. coli* and the sterile feces–barium sulfate combination, the intraperitoneal $pO_2$ elevation was seen through 4 hours, followed by a decline such that by 6 hours intraperitoneal $pO_2$ had decreased significantly below controls to 32 ± 3.4 mmHg ($p < 0.01$). Rats infected with *E. coli, B. fragilis,* and the adjuvant demonstrated an increase in intraperitoneal $pO_2$ through 5 hours ($p < 0.01$), followed by a rapid decline to 44 ± 3.1 mmHg, significantly less than control ($p < 0.01$) at 6 hours (Fig. 7). Intraperitoneal pH was again 7.40 ± 0.01 at the start in all groups. At 6 hours intraperitoneal pH was significantly different from controls ($p < 0.01$) in the *E. coli* and SFA adjuvant group, where intraperitoneal pH at 6 hours was 7.15 ± 0.02, and in the *E. coli, B. fragilis,* and adjuvant group where it was 7.23 ± 0.02 (Table 2). Arterial $pO_2$ was not different among any group and controls at time zero. In all infected groups, a mild increase was noted by 1 hour and was maintained throughout all 6 hours, with no difference between groups ($p > 0.1$). As previously noted the control group displayed a slight decrease in arterial $pO_2$ at 5 and 6 hours, yielding a slight but significant ($p < 0.05$) difference compared to the experimental groups (Fig. 8). Through 5 hours arterial pH was consistent and not different from controls ($p > 0.1$). At 6 hours only, the arterial pH was significantly lower ($p < 0.01$) in rats inoculated with *E. coli* and the adjuvant (7.35 ± 0.02) or *E. coli, B. fragilis,* and the adjuvant (7.37 ± 0.01) than in controls (7.42 ± 0.02) (Fig. 9). On culture fewer than $10^2$ cfu of bacteria, all gram-positive cocci and diptheroids were recovered from rats inoculated with the sterile feces–barium sulfate combination alone. *E. coli* was recovered in significantly greater numbers ($p < 0.01$) when mixed with either the SFA adjuvant or the adjuvant and *B. fragilis* when compared to groups with *E. coli* alone or with only *B. fragilis*. The number of recoverable *B. fragilis* was not significantly different between groups (Fig. 10).

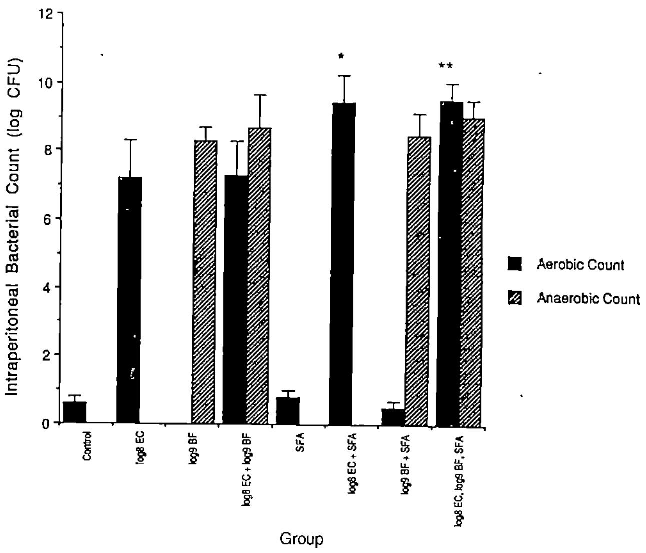
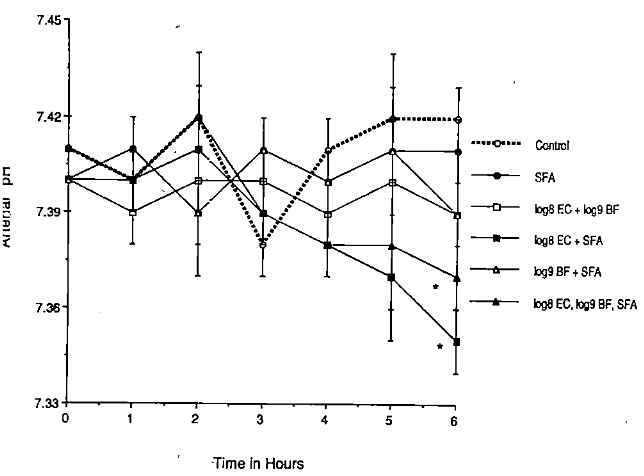


FIG. 10. Intraperitoneal *Escherichia coli* (EC) and *Bacteroides fragilis* (BF) recovered when animals were killed in selected monomicrobial, polymicrobial, and sterile feces adjuvant (SFA)-aided groups. *Indicates p ≤ 0.05 *versus* log 8 EC without SFA, **Indicates p ≤ 0.05 *versus* log 8 EC and log 9 BF without SFA.



IG. 9. Effect of mixed *Escherichia coli* (EC) and *Bacteroides fragilis* BF) or sterile feces adjuvant (SFA) inocula on arterial pH. *Indicates p ≤ 0.05 *versus* uninfected controls; error bars indicate standard error of he mean.

## Discussion

Neither the peritoneal environment nor the response to various insults have been well characterized. Of particular interest in this study are the changes in local $pO_2$, especially as it affects the growth of aerobic and anaerobic bacteria and their interactions with adjuvant matter, and pH, which is known to be markedly decreased in the presence of ischemic or necrotic tissue.

Although it has been assumed, given the permeability characteristics of the peritoneum, that the peritoneal $pO_2$ under normal conditions approximates the capillary $pO_2$, this has not been easily demonstrated. In 1974 Klossner[17] described a technique for its intermittent measurement by the implantation of silastic tubing, which is freely gas permeable,[14] in the peritoneum, and the instillation of anoxic saline into this tubing. After an equilibration time, the saline was removed and assessed for $pO_2$ and $pCO_2$

using standard techniques. In 1983 Gottrup[15] developed a method for the continuous direct measurement of tissue oxygen tension using silastic tubing and oxygen polarography. We adapted a combination of these two means in our studies and obtained reproducible, consistent results, with a mean intraperitoneal $pO_2$ of 52 to 53 mmHg in untreated controls throughout the 6 hours of study. These values were consistently 10 to 11 mmHg higher than those cited by Klossner and probably were influenced by the specific kinds of silastic catheters used and different equilibration times: Klossner using only two minutes, a value derived from *in vitro* studies, and the method used in this study of continuous monitoring of intraperitoneal $pO_2$ until stabilization at each measurement, a procedure often taking 10 minutes or longer. This technique was used because of simplicity, durability, and the integration of values over a wider area of concern. The question of actual cellular oxygen tension, of course, remains unanswered. The animal model used here also appeared to be more reproducible than that used by Renvall[13] because peritonitis was achieved in all animals studied and was produced with a known inoculum. If one considers their model to be one of overwhelming infection analogous to the sterile stool, *E. coli*, and *B. fragilis* mixture used here, the results are somewhat similar in that they noted a steady decline in intraperitoneal $pO_2$.

It would be natural to assume that the intraperitoneal pH would approximate neutrality before catheter implantation and after 6 hours of study in the control group. This was observed in the control animals with a pH of 7.4 at initial laparotomy and 7.38 at 6 hours in uninfected animals. As with Renvall's earlier experiments, a decline in intraperitoneal pH was noted with severe peritonitis.

Although monomicrobial, polymicrobial nonadjuvant-aided peritonitis, or pure sterile fecal peritonitis are rare clinical entities, we studied each alone or as combinations as the components of polymicrobial, fecal peritonitis. In the sublethal inocula used here, infections induced with *E. coli* or *B. fragilis* alone, or in combination without sterile fecal adjuvant, effected an increased intraperitoneal $pO_2$ within 1 hour that persisted through the duration of study, yet no significant alteration in intraperitoneal pH was seen. The same effects were seen with the introduction of sterile feces alone. The lone exception was $10^6$ *B. fragilis*, which produced no changes. These data suggest that the peritoneal inflammatory response is a stereotypic response to peritoneal irritation, with the arterial $pO_2$ unchanged or only slightly increased, indicating a decreased gradient between the vascular and peritoneal spaces. The cause of this phenomenon is not specifically addressed in this study, but it can be speculated that an enhancement of either mesothelial oxygen permeability or oxygen delivery occurs, most likely secondary to insult-induced hyperemia.

Conversely inocula of *E. coli* well above the $LD_{50}$ induced a late and significant decrease in the intraperitoneal $pO_2$, despite a stable arterial $pO_2$. Both the intraperitoneal and arterial pH also decline, although the former to a much greater extent than the latter. These findings indicate an increased arterial–peritoneal gradient of oxygen and hydrogen ions. Again these studies do not elucidate the exact etiology of these findings, but there are three possible explanations for this induced local hypoxia and acidity. First the bacteria present may proliferate rapidly enough to exceed the delivery of substrates and the removal of waste products. Second the local host response *via* immune cells also could use local substrates and produce by-products at an increased rate. Third a generalized splanchnic vasoconstriction, secondary to local or systemic factors, could impede the delivery of oxygen and other nutrients to the site of inflammation. Whatever mechanism is present in these overwhelming infections, an environment is produced that encourages the proliferation of anaerobes and impedes the function of host-defense immune cells.

Fecal peritonitis, especially as a prelude to abscess formation, is a markedly more complex situation that is still not completely understood. Animal models have given some details of both host defense[16,18] and bacterial contributions[5,8,10] to this process. In early stages the host response includes the lymphatic absorption of bacteria, the influx of polymorphonuclear neutrophils and macrophages, and the release of opsonins, vasoactive substances, various enzymes, and fibrin-rich fluids. If the infectious insult is not quickly cleared or destroyed, fibrous adhesions form between serosal surfaces, producing loculations that eventually can lead to well-defined abscesses. The role of bacteria has similarly been examined clinically and experimentally.[1-4] Most abscesses are polymicrobial, and, in fact, it is close to impossible to induce abscesses experimentally with a pure culture of a single bacterium, except under very special, and usually artificial, conditions. Furthermore the bacterial synergy between aerobic and anaerobic bacteria in experimental models has been well described:[5] aerobes, usually *E. coli*, are associated with early death and positive blood cultures, while anaerobes, usually *B. fragilis*, are required for consistent intra-abdominal abscess formation.[6,7] The mechanisms underlying this interaction may include the production of growth factors, the release of substances interfering with the immune response, for example, succinate, and alteration of the local environment, *e.g.*, pH, $pO_2$, or redox potential. Various particulate adjuvants substances have also been shown to alter significantly the outcome of peritonitis, including sterile feces,[10] necrotic tissue,[19] barium sulfate,[8] and bran.[10] Consistent abscess formation, even with a mixed inoculum, also is quite difficult without the presence of adjuvants; whether this is due to decreased bacterial clearance, augmented bacterial growth, or both is also unclear. This is the question we wished to examine, using a system devised to produce an environment conducive to the formation of abscesses.

Significantly decreased intraperitoneal $pO_2$ and pH values by 6 hours in the presence of *E. coli*, *B. fragilis*, and SFA were noted in this study. Although this is similar to the environment previously found in mature abscesses, the rapidity with which these changes occur was somewhat unexpected and could not be attributed to a well-localized infection, but, rather, to a generalized condition. The pathogenesis of these changes is clarified somewhat by the observation that the same alterations occur in the presence of *E. coli* and SFA alone, but not with *B. fragilis* and SFA; it would appear that it is the combination of an aerobe and particulate matter that accounts for the hypoxic/acidic milieu. The implication regarding bacterial synergy is obvious.

Regardless of the presence of anaerobes, *E. coli* was noted to be recovered in significantly greater numbers when SFA was added, probably through decreased clearance leading to more viable, reproducing bacteria. The increased oxygen consumption and production of metabolites of these aerobes yields an environment able to promote anaerobic growth. Although *E. coli* proliferation may enhance *B. fragilis* growth and abscess formation seemingly by producing anaerobic conditions, it is still possible that *E. coli* could produce other substances that directly promote anaerobic growth or blunt the immune response. Nevertheless these rapid changes in local environment must be taken into account in the further study of intraperitoneal infection.

The effects of bacteria and particulate matter and their interactions on early and late intra-abdominal infections are complex. These experiments studied the local environment during early peritonitis only but have demonstrated that under certain conditions known to favor the formation of abscesses, such as the presence of *E. coli* and sterile feces, the local environment is altered rapidly. A marked decline in both intraperitoneal $pO_2$ and pH appears to enhance the ability of anaerobes to multiply and produce chronic mixed infections that are seen commonly in the clinical arena.

## References

1. Altemeier WA. The bacterial flora of acute perforated appendicitis with peritonitis: a bacteriologic study based upon one hundred cases. Ann Surg 1938; 107:517–528.
2. Altemeier WA, Culbertson WR, Fuller WD, et al. Intra-abdominal abscesses. Am J Surg 1973; 125:70–79.
3. Lorber B, Swenson RM. The bacteriology of intra-abdominal infections. Surg Clin North Am 1975; 55:1349–1354.
4. Stone HH, Kolb LD, Geheber CF. Incidence and significance of intraperitoneal anaerobic bacteria. Ann Surg 1976; 181:705–715.
5. Onderdonk AB, Bartlett JG, Louie T, et al. Microbial synergy in experimental intraabdominal abscess. Infect Immun 1976; 13: 22–28.
6. Onderdonk AB, Kasper DL, Cisneros RL, et al. The capsular polysaccharide of *Bacteroides fragilis* as a virulence factor: comparison of the pathogenic potential of encapsulated and unencapsulated strains. J Infect Dis 1977; 136:82–89.
7. Weinstein WM, Onderdonk AB, Bartlett JG, et al. Antimicrobial therapy of experimental intraabdominal sepsis. J Infect Dis 1975; 132:282–286.
8. Weinstein WM, Onderdonk AB, Bartlett JG, et al. Experimental intra-abdominal abscesses in rats: development of an experimental model. Infect Immun 1974; 10:1250–1255.
9. Dunn DL, Rotstein OD, Simmons RL. Fibrin in peritonitis: IV. Synergistic intraperitoneal infection due to *Escherichia coli* and *Bacteroides fragilis* within fibrin clots. Arch Surg 1984; 119:149–144.
10. Nulsen MF, Finlay-Jones JJ, Skinner JM, et al. Intra-abdominal abscess formationin mice: quantitative studies on bacteria and abscess potentiating agents. Br J Exp Path 1983; 64:345–353.
11. Walker CB, Williams TD. Use of semisolid agar for initiation of pure *Bacteroides fragilis* infection in mice. Infect Immun 1976; 14:721–725.
12. Mackowiak PA. Microbial synergy in human infections. N Engl J Med 1978; 298:83–86.
13. Renvall S, Niinkoski J. Intraperitoneal oxygen and carbon dioxide tensions in experimental adhesion disease and peritonitis. Am J Surg 1975; 130:286–292.
14. Niinkoski J, Hunt TK. Measurement of wound oxygen with implanted silastic tube. Surgery 1972; 71:22–26.
15. Gottrup F, Firman R, Chang N, et al. Continuous direct tissue oxygen tension measurement by a new method using an implanted silastic tonometer and oxygen polarography. Am J Surg 1983; 146:399–403.
16. Dunn DL, Barke RA, Knight NB, et al. Role of resident macrophages, peripheral neutrophils, and translymphatic absorption in bacterial clearance from the peritoneal cavity. Infect Immun 1985; 49: 257–264.
17. Klossner J, Kivisaari J, Niinkoski J. Oxygen and carbon dioxide tensions in the abdominal cavity and colonic wall of the rabbit. Am J Surg 1974; 127:711–715.
18. Dunn DL, Barke RA, Ewald DC, et al. Macrophages and translymphatic absorption represent the first line of host defense of the peritoneal cavity. Arch Surg 1987; 122:105–110.
19. Wichterman KA, Baue AE, Chaudry IH. Sepsis and septic shock—a review of laboratory models and a proposal. J Surg Res 1980; 29:189–201.

# Elevated Plasma Endothelin-1 Concentrations Are Associated with the Severity of Illness in Patients with Sepsis

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**Plasma immunoreactive endothelin-1 concentrations were determined by radioimmunoassay in 11 septic patients during the first 24 hours after the development of the sepsis syndrome in 15 nonseptic postoperative patients studied 24 hours after open heart surgery and in 14 healthy volunteers. Mean endothelin-1 plasma concentrations were significantly ($p < 0.001$) increased in septic patients (19.9 ± 2.2 pg/mL, mean ± standard error) compared to concentrations found in postoperative cardiac patients (11.9 ± 0.7 pg/mL) or in healthy volunteers (6.1 ± 0.3 pg/mL). In septic patients elevated plasma concentrations of endothelin-1 were inversely correlated with cardiac index ($r = -0.80$, $p < 0.005$) and positively correlated the severity of illness as documented by APACHE II score ($r = 0.74$, $p < 0.01$) and plasma creatinine levels ($r = 0.80$, $p < 0.005$). No such correlations were found in postoperative cardiac patients. These results indicate that endothelin-1 concentrations are correlated with the severity of illness and depression of cardiac output in patients with sepsis.**

ENDOTHELIN, A NEWLY described potent vasoconstrictor peptide[1] recently was isolated from the culture supernatant of porcine[2] and human[3] endothelial cells. In animal studies administration of exogenous endothelin-1 was reported to produce intense vasoconstriction in various vascular beds[4-7] and to induce the release of prostacyclin and endothelium-derived relaxing factor.[8] We recently demonstrated that plasma and pulmonary lymph concentrations of endothelin-1-like immunoreactivity (LI) were increased during sustained endotoxemia in sheep, whereas no detectable plasma or lymph levels of endothelin-1-LI were found in normal sheep.[9] Endotoxin-induced endothelial cell injury is the most probable cause of the observed increased circulating endothelin-1-LI concentration. The endogenous release of this vasoconstrictor peptide and its possible role in sepsis have not been studied yet in humans, whereas some evidence was produced that endothelin may be involved in the pathophysiology of acute myocardial infarction[10] and in uremia[11] in humans. In the present study, we measured the plasma endothelin-1-LI in patients with a sepsis syndrome[12] and compared it with plasma endothelin-1 concentrations measured in patients after open heart surgery and in healthy human volunteers.

## Methods

Eleven patients with a diagnosis of the sepsis syndrome[12] (age, 56 ± 6 years [mean ± standard error]; range, 21 to 75 years; 76 ± 5 kg body weight, Table 1), 15 nonseptic patients (age, 53 ± 8 years; range, 24 to 83 years; 75.4 ± 1.7 kg body weight) studied 24 hours after open heart surgery, and 14 healthy volunteers (age, 44 ± 6 years; range, 32 to 55 years; 72.5 ± 2.1 kg body weight) were included in the study. The study was approved by the Committee for Ethics in Human Research of our institution and informed consent was obtained from all patients and volunteers.

In patients with the sepsis syndrome, arterial blood samples were taken during the first 24 hours after the diagnosis of the septic syndrome. The APACHE II score,[13], derived from 12 clinical and laboratory variables, age, and previous health status were determined for all

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TABLE 1. *Characteristics of Patients*

| Patient | Age (yrs) | Sex (M/F) | Weight (kg) | APACHE II score | Blood cultures | Creatinine μmol/L | WBC × $10^9$/L | PLT × $10^9$/L | Diagnosis | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38 | M | 78 | 15 | — | 34 | 25.0 | 107 | Acute pancreatitis, peritonitis | D |
| 2 | 74 | M | 90 | 29 | *E. coli* | 424 | 18.0 | 15 | Infected hip prosthesis | S |
| 3 | 54 | M | 74 | 14 | — | 82 | 14.6 | 36 | Postop Ca esophagus, ARDS | D |
| 4 | 65 | M | 78 | 14 | *Staph. aureus* | 55 | 16.9 | 104 | Postop Ca pancreas, peritonitis | D |
| 5 | 75 | M | 50 | 20 | — | 164 | 15.0 | 243 | Acute peritonitis | D |
| 6 | 67 | M | 84 | 27 | Proteus | 266 | 3.5 | 5 | Postop meningitis | D |
| 7 | 38 | M | 75 | 7 | *Staph. aureus* | 86 | 6.0 | 69 | Multiple trauma, ARDS | S |
| 8 | 21 | F | 60 | 15 | *Staph. aureus* | 55 | 3.0 | 54 | Multiple trauma, ARDS | S |
| 9 | 76 | M | 86 | 26 | Pseudomonas | 398 | 20.1 | 210 | Postop Ca bile duct, peritonitis | S |
| 10 | 63 | M | 95 | 21 | *Staph. aureus* | 357 | 13.9 | 47 | Ruptured aortic aneurysm | S |
| 11 | 60 | M | 80 | 15 | *Staph. aureus* | 247 | 26.4 | 82 | Acute pancreatitis | S |

WBC, white blood cell count; PLT, platelets; ARDS, adult respiratory distress syndrome; Ca, carcinoma; D, died; S, survived.

septic patients at the time of admission to the intensive care unit. None of the patients were receiving vasoactive or inotropic drugs, except for a low dose of dopamine (2 to 3 μg/kg · min). Patients studied after open heart surgery were not receiving any vasoactive or inotropic support at the time of the study and had been hemodynamically stable for at least 8 hours before blood samples were taken. Blood samples were collected in tubes containing 5 mg of edetic acid (ethylenedinitrilo tetraacetic acid) and the plasma separated by centrifugation. Plasma samples were stored at −70 C until analysis.

After extraction of plasma in acid-ethanol, endothelin-1–LI in plasma was determined by radioimmunoassay using a specific antiserum (diluted 1:60,000) raised in rabbits against porcine endothelin-1. The cross-reactivity to other endothelin peptides are (endothelin-1 expressed as 100%): endothelin-2, 64%; endothelin-3, 7%; and big endothelin-1, 90%. The antiserum shows no cross-reactivity to other peptides such as atrial natriuretic peptide, vasopressin, or angiotensin I, II, and III. Endothelin-1 labeled with $^{125}$I was used as tracer and porcine endothelin-1 as a standard. The assay was incubated at +4 C in 0.1 mol/L (molar) phosphate buffer, pH 7.4, containing 0.1% bovine serum albumin and 0.1% Triton-X-100. Bound and free fractions were separated using a secondary antibody.[14] The detection limit of the assay is 0.75 fmol/tube.

All recorded variables (mean ± SE) were compared between the three groups of patients and volunteers using a one-way analysis of variance followed by Duncan's multicomparisons test. A p value < 0.05 was considered statistically significant.

## Results

Hemodynamic, respiratory, and plasma lactate values of patients are summarized in Table 2. Plasma endothelin-1–LI concentrations for both groups of patients and healthy volunteers are shown in Figure 1. In volunteers, the mean plasma endothelin- 1–LI level was 6.1 ± 0.3 pg/mL. Patients studied 24 hours after open heart surgery had a significantly increased mean plasma concentration of endothelin-1–LI compared to volunteers (11.9 ± 0.7 pg/mL, $p < 0.0001$). The mean plasma endothelin-1–LI level measured in patients with the sepsis syndrome also was significantly increased (19.9 ± 2.2 pg/mL) compared to volunteers ($p < 0.0001$) as well as compared to postoperative cardiac patients ($p = 0.0004$). No difference in plasma endothelin-1–LI level was observed in the septic group between patients with or without positive blood cultures. However the three patients with a gram-negative septicemia had a significantly greater plasma level of endothelin-1–LI than the other patients in the septic group (26.8 ± 4.6 *versus* 17.3 ± 1.8 pg/mL, $p < 0.005$). The relationship between plasma endothelin-1–LI concentrations and cardiac index for both patient groups is shown in Figure 2. In septic patients, there was a significant inverse linear correlation between plasma endothelin-1–LI levels and cardiac index ($r = -0.80$, $p < 0.005$). In these patients endothelin-1–LI plasma concentrations were significantly correlated with APACHE II score ($r = 0.74$, $p < 0.01$) and plasma creatinine levels ($r = 0.80$, $p < 0.005$), but not with plasma lactate levels, mean systemic arterial pressure, systemic vascular resistance index, intrapulmonary venous admixture, or alveolar–arterial oxygen gradient/inspired oxygen fraction ratio. In postoperative cardiac patients, no such correlations were found between plasma endothelin-1–LI levels and cardiac index (Fig. 2), plasma creatinine levels, and other hemodynamic or respiratory variables.

## Discussion

The results of the present study show that plasma endothelin-1–LI levels are significantly increased in patients with the sepsis syndrome compared to the values found in postoperative nonseptic patients or in healthy volunteers. These data also provide evidence that in septic pa-

TABLE 2. *Hemodynamic, Respiratory, Plasma Lactate, and Endothelin Values of Patients*

| Patient | MAP (mmHg) | MPAP (mmHg) | CI ($l \cdot min^{-1} \cdot m^{-2}$) | CVP (cm $H_2O$) | PCWP (cm $H_2O$) | $AaDO_2/FIO_2$ (kPa) | Qs/Qt (%) | Lactate (mmol/L) | Endothelin (pg/mL) |
|---|---|---|---|---|---|---|---|---|---|
| Patients with a septic syndrome | | | | | | | | | |
| 1 | 77 | 36 | 7.02 | 14 | 16 | 67 | 60 | 1.06 | 14.27 |
| 2 | 56 | 24 | 2.57 | 12 | 10 | 69 | 30 | 2.70 | 23.29 |
| 3 | 78 | 29 | 5.91 | 11 | 12 | 57 | 30 | 2.60 | 16.57 |
| 4 | 61 | 17 | 6.18 | 8 | 8 | 69 | 44 | 3.52 | 15.32 |
| 5 | 67 | 25 | 4.00 | 9 | 14 | 48 | 30 | 2.37 | 18.71 |
| 6 | 78 | 25 | 3.57 | 6 | 11 | 57 | 29 | 6.36 | 21.20 |
| 7 | 81 | 27 | 7.08 | 13 | 11 | 59 | 33 | 1.35 | 7.85 |
| 8 | 72 | 31 | 5.22 | 9 | 8 | 68 | 40 | 3.56 | 17.79 |
| 9 | 63 | 23 | 3.35 | 14 | 20 | 51 | 25 | 2.84 | 35.87 |
| 10 | 59 | 27 | 4.07 | 12 | 16 | 60 | 29 | 1.95 | 23.02 |
| 11 | 55 | 24 | 3.06 | 12 | 11 | 67 | 29 | 6.15 | 24.56 |
| x ± SE | 68 ± 3 | 26 ± 1 | 4.7 ± 0.5 | 11 ± 1 | 12 ± 1 | 61 ± 2 | 35 ± 3 | 2.8 ± 0.5 | 19.9 ± 2.2 |
| Nonseptic postoperative cardiac patients | | | | | | | | | |
| x ± SE | 77 ± 2* | 22 ± 2 | 2.4 ± 0.1* | 12 ± 1 | 13 ± 1 | 35 ± 2* | 19 ± 1* | 1.7 ± 0.2* | 11.9 ± 0.7* |

* $p < 0.05$ from septic patients.

n = 11 in septic patient group and n = 15 in nonseptic postoperative cardiac patients.

MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; $AaDO_2/FIO_2$, alveolar arterial oxygen gradient/inspired oxygen fraction; Qs/Qt, intrapulmonary venous admixture.

tients the plasma concentration of endothelin-1–LI correlates with the severity of illness. We found that patients with the greatest severity of disease at the time of the study as measured by the APACHE II score had the highest levels of endothelin-1–LI. In addition, we found an inverse correlation between plasma endothelin-1–LI levels and cardiac index for comparable cardiac filling pressures (Fig. 2). It has been proposed that an elevated cardiac output is needed in septicemia to maintain an effective oxygen delivery.[15] In the present study, patients with the greatest endothelin-1–LI levels had the highest APACHE II scores, but their cardiac index was not elevated. The fact that there was an inverse correlation between plasma endothelin-1–LI levels and cardiac index, but no significant relationship between plasma endothelin-1–LI levels and systemic vascular resistance index suggests that in humans with sepsis, endothelin-1 might be one of the

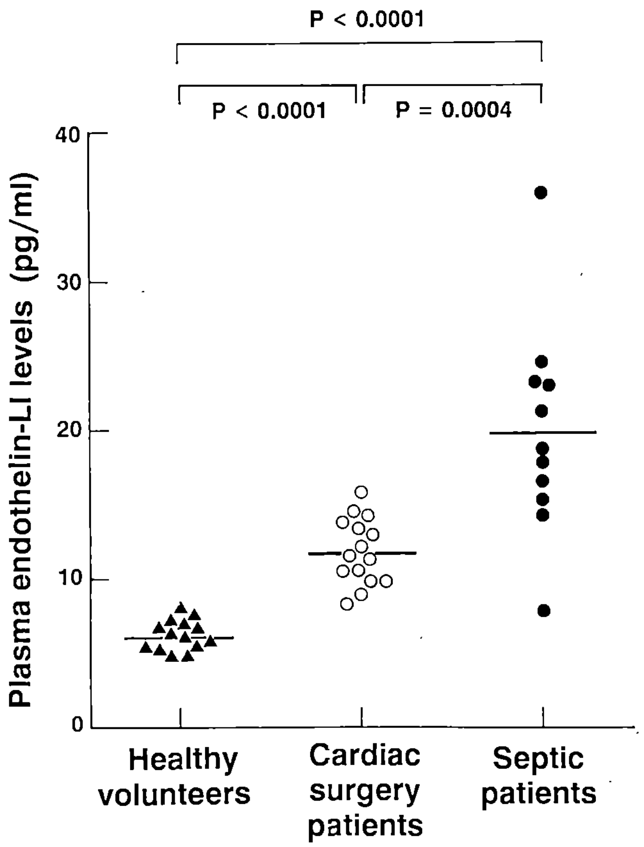

FIG. 1. Plasma endothelin concentrations.

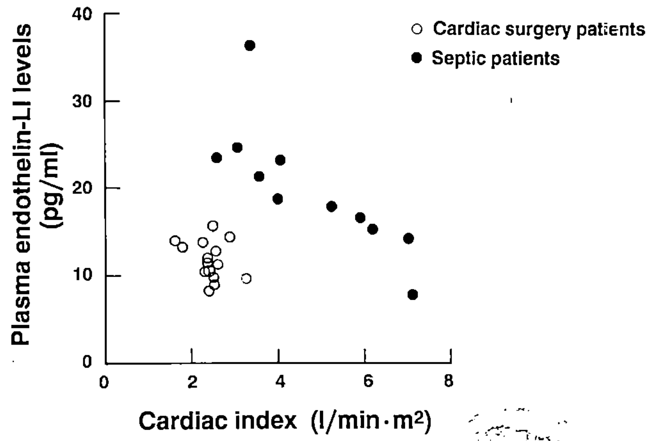

FIG. 2. Relationship between plasma endothelin concentrations and cardiac index in both groups of patients.

described circulating myocardial depressant substances[16] rather than acting as an effective systemic vasoconstrictor. Interestingly sarafotoxins that represent endothelinlike peptides in some snake venom exert strong cardiac toxicity due to prolonged coronary vasospasm.[17] Increased plasma and cardiac tissue concentrations of endothelin-1 were also reported in an experimental model of myocardial infarction.[18] Neutralizing endogenous endothelin-1 with administration of monoclonal antibodies against endothelin-1 resulted in a significant decrease of the infarction size, indicating that endogenous endothelin-1 is one of the factors that contribute to the extension of myocardial infarction.[18] In our study high levels of endothelin-1–LI were associated with increased plasma creatinine levels and it has been suggested that endothelin-1 also may play an important role in the development of acute renal failure.[19,20]

Increased plasma endothelin-1–LI concentrations measured in septic patients probably are not only due to an acute stress response, as has been reported after major abdominal surgery.[21] Endothelin-1–LI levels in these patients were significantly greater than those measured in patients after major cardiac surgery with extracorporeal bypass and in healthy volunteers. Plasma endothelin-1 concentrations measured in our volunteers were similar to that recently found by Davenport et al.[22] Elevated plasma endothelin-1–LI in sepsis is probably the result of an endotoxin-induced release of endothelin-1 by injured endothelial cells. Previously it was reported in rats that endotoxin stimulates endothelin release *in vivo*.[23] Similarly we found in awake sheep a clearcut increase of endothelin-1–LI levels in pulmonary lymph and plasma during sustained endotoxemia.[9] It also has been demonstrated that *E. coli* endotoxin induces the production of endothelin from cultured bovine endothelials cells.[23] Gram-negative bacteria may themselves produce precursors of endothelin.[24] These animal and *in vitro* results correlate with our human data in which the three patients with gram-negative septicemia had the highest plasma endothelin-1–LI evels. In conclusion our investigation demonstrates that endothelin-1–LI concentrations are correlated with the severity of illness and depression of cardiac output in paients with sepsis. Further clinical studies are needed to define better the precise role of endothelin in the pathophysiology of sepsis.

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## References

1. Inoue A, Yanagisawa M, Kimura S, et al. The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. Proc Natl Acad Sci USA 1989; 86:2863–2867.
2. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988; 332:411–415.
3. Itoh Y, Yanagisawa M, Ohkubo S, et al. Cloning and sequence analysis of cDNA encoding the precursor of a human endothelium-derived vasoconstrictor peptide, endothelin: identity of human and porcine endothelin. FEBS Lett 1988; 231:440–444.
4. Brain SD, Tippins JR, Williams TJ. Endothelin induces potent microvascular constriction. Br J Pharmacol 1988; 95:1005–1007.
5. Pernow J, Boutier JF, Franco-Cereceda A, et al. Potent selective vasoconstrictor effects of endothelin in the pig kidney in vivo. Acta Physiol Scand 1988; 134:573–574.
6. Minkes RK, McMillan LA, Bellan JA, et al. Analysis of regional responses to endothelin in hindquarters vascular bed of cats. Am J Physiol 1989; 256:H598–H602.
7. Lippton HL, Hauth TA, Summer WR, et al. Endothelin produces pulmonary vasoconstriction and systemic vasodilatation. J Appl Physiol 1989; 66:1008–1012.
8. De Nucci G, Thomas R, D'Orleans-Juste P, et al. Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci USA 1988; 85:9797–9800.
9. Morel DR, Lacroix JS, Hemsen A, et al. Increased plasma and pulmonary lymph levels of endothelin during endotoxin shock. Eur J Pharmacol 1989; 167:427–428.
10. Miyauchi T, Yanagisawa M, Tomizawa T, et al. Increased plasma concentrations of endothelin-1 and big endothelin-1 in acute myocardial infarction. Lancet 1989; i:53–54.
11. Koyama H, Nishzawa Y, Morii H, et al. Plasma endothelin levels in patients with uraemia. Lancet 1989; i:991–992.
12. Bone RC, Fisher CJ, Clemmer TP, et al. Sepsis syndrome: a valid clinical entity. Crit Care Med 1989; 17:389–393.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13:818–829.
14. Theodorsson-Norheim E, Hemsen A, Lundberg JM. Radioimmunoassay for neuropeptide Y (NPY): chromatographic characterization of immunoreactivity in plasma and tissue extracts. Scand J Clin Lab Invest 1985; 54:355–365.
15. Wolf Y, Cotev S, Perel A, et al. Dependence of oxygen consumption on cardiac output in sepsis. Crit Care Med 1987; 15:198–202.
16. Parrillo JE, Burch C, Shelhamer JH, et al. A circulating myocardial depressant substance in humans with septic shock: septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest 1985; 76:1539–1553.
17. Lee SY, Lee CY, Chen YU, et al. Coronary vasospasm as the primary cause of death due to the venom of the burrowing asp, Atractaspis engaddenis. Toxicon 1986; 24:285–291.
18. Watanabe T, Suzuki N, Shimamoto N, et al. Endothelin in myocardial infarction. Nature 1990; 344:114.
19. Firth JD, Ratcliffe PJ, Raine AE, et al. Endothelin: an important factor in acute renal failure? Lancet 1988; ii:1179–1182.
20. Tomita K, Ujiie K, Nakanishi T, et al. Plasma endothelin levels in patients with acute renal failure. N Engl J Med 1989; 321:1127.
21. Saito T, Yanagisawa M, Miyauchi T, et al. Endothelin in human circulating blood: effect of major surgical stress (Abstract). Jpn J Pharmacol 1989; 49:215P.
22. Davenport AP, Ashby MJ, Easton P, et al. A sensitive radioimmunoassay measuring endothelin-like immunoreactivity in human plasma: comparison of levels in patients with essential hypertension and normotensive control subjects. Clinical Science 1990; 78:261–264.
23. Sugiura M, Inagami T, Kon V. Endotoxin stimulates endothelin-release in vivo and in vitro as determined by radioimmunoassay. Biochem Biophys Res Commun 1989; 161:1220–1227.
24. Watanabe T, Itoh Y, Ogi K, et al. Synthesis of human endothelin-1 precursors in Escherichia coli. FEBS Lett 1989; 251:257–260.

# Blockade of Prostaglandin Production Increases Cachectin Synthesis and Prevents Depression of Macrophage Functions After Hemorrhagic Shock

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**Although hemorrhage severely depresses macrophage functions, it is not known whether the increased TNF-$\alpha$ or $PGE_2$ production is responsible for it. To study this C3H/HeN mice were bled to mean blood pressure of 35 mmHg for 60 minutes, resuscitated, and treated with either ibuprofen (1.0 mg/kg body weight) or vehicle (saline). Hemorrhage increased plasma prostaglandin $E_2$ ($PGE_2$) levels by 151.7% ± 40.0% ($p < 0.05$) and significantly decreased peritoneal macrophage (pM$\phi$) antigen presentation (AP) by 60.5% ± 7.3%, Ia expression by 52.3% ± 7.6%, and interleukin-1 (IL-1) synthesis by 60.5% ± 12.3% compared to shams. However ibuprofen treatment reduced $PGE_2$ plasma levels by 61.3% ± 12.1% and significantly increased AP (+237.0% ± 95.3%), Ia expression (+72.8% ± 27.5%), IL-1 synthesis (+235.7% ± 134.7%), and cachectin synthesis (+485.8% ± 209.0%) compared to vehicle-treated animals. These results indicate that prostaglandins but not cachectin are involved in the suppression of pM$\phi$ functions following hemorrhage because blockade of prostaglandin synthesis improved depressed macrophage functions despite enhanced cachectin synthesis.**

SIMPLE HEMORRHAGE CAUSES a severe suppression of macrophage,[1] T-lymphocyte,[2] and B-lymphocyte[3] functions. The suppression of macrophage antigen presentation,[4] major histocompatibility complex (MHC) class II (Ia) expression,[4] and interleukin-1 (IL-1)[5] production after hemorrhage results in a depression of adequate T-lymphocyte induction, lymphokine production, and consequently may contribute to the enhanced susceptibility to sepsis.[6] The mechanisms and potential mediators involved in the suppression of the immune responses after hemorrhage are not clearly understood. It has been suggested that after mechanical trauma[7] or burn injury,[8] prostaglandins of the E series, potent suppressor factors of cellular[9] and humoral immunity,[10] may play a detrimental role in inducing a defective immune response. In support of this suggestion are recent studies[11] that indicate that cyclooxygenase inhibitors can significantly improve the depressed T-cell proliferation and IL-2 synthesis *in vitro* following major mechanical trauma. Furthermore studies by Faist et al.[12] demonstrated beneficial effects of *in vivo* indomethacin administration on different parameters of cellular immunity after major surgery.

Although the above studies indicate that prostaglandin $E_2$ ($PGE_2$) may be responsible for the depression of immunologic function after trauma, it is not known whether $PGE_2$ is involved in the induction of the observed immunosuppression after simple hemorrhage. In addition it is not known whether the observed alterations in cachectin (TNF-$\alpha$) synthesis,[13] a major mediator of the inflammatory response, are closely related to alterations of $PGE_2$ production. *In vitro* studies of Kunkel et al.[14] demonstrated that $PGE_2$ is a potent downregulator of tumor necrosis factor alpha (TNF-$\alpha$) gene expression and synthesis. Whether alterations in TNF-$\alpha$ synthesis are beneficial or immunosuppressive is not clear. Studies investigating effects of TNF infusions on the host are controversial and the effects of TNF seem to be dose dependent. Sheppard et al.[15] demonstrated a decreased mortality rate after endotoxemia and sepsis following pretreatment with TNF, while studies by Tracey et al.[16] showed that TNF administration induced tissue injury and a shocklike state.

The aim of this study, therefore, was to determine whether arachidonic acid metabolites and/or increased cachectin production are involved in the suppression of macrophage functions such as antigen presentation, Ia

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expression, and IL-1 synthesis after hemorrhage, and whether the systemic administration of the cyclooxygenase inhibitor ibuprofen after hemorrhage has any beneficial effects on macrophage functions.

## Materials and Methods

### *Animals*

Inbred C3H/HeN male mice (Charles River Labs., Portage, MI), 6 to 8 weeks old, weighing 20 to 25 g were used in all experiments. Animals were fasted 12 hours before the experiments and were allowed to have food *ad libidum* thereafter. The care of all animals was in accordance with the guidelines set forth by the Animal Welfare Act and with the Guide for the Care and Use of Laboratory Animals, National Institutes of Health Publications.

### *Hemorrhage Model*

Hemorrhage was induced according to the method of Stephan et al.[2] Briefly, mice were slightly anesthetized with methoxyflurane and restrained in supine position. Both femoral arteries were catheterized with 10 polyethylene tubing under aseptic conditions using a minimal dissection technique. Mice were heparinized (150 U/kg/body weight beef lung heparin [Upjohn Labs., Kalamazoo, MI]) and allowed to awaken. Blood pressure (BP) was constantly measured by attaching one of the catheters to a strain gauge pressure transducer coupled to a polygraph. The animals were bled (~0.78 ± 0.12 mL/animal; ~50% of estimated mouse blood volume) through the second catheter to a mean arterial BP of 35 ± 5 mmHg (mean BP before hemorrhage, 94.4 ± 8.3 mmHg). This BP was maintained for 60 minutes followed by infusion of the hed blood and Ringer's lactate solution (twice the shed blood volume) to provide adequate fluid resuscitation. In buprofen-treated animals, ibuprofen (Sigma Chemical Co., St. Louis, MO) was administered systemically as bolus 1 mg/kg/body weight) immediately after reinfusion of he shed blood. Vehicle-treated hemorrhaged animals received an equal volume of saline. After resuscitation the catheters were removed and the groin incisions closed. There were no deaths in either the vehicle-treated or ibuprofen-treated groups. Furthermore no significant changes n BP were detected after ibuprofen administration. Conrol (sham) animals underwent the same anesthetic and urgical procedures, including ligation of both femoral arteries, but hemorrhage was not induced.

### *Preparation of Peritoneal Macrophages*

Mice were killed 24 hours after hemorrhage and resuscitation. Peritoneal macrophages (pMϕ) were harvested by lavage using 10 mL of ice-cold Click's medium (Irvine Scientific, Santa Ana, CA). Cells were washed once (280*g*, 15 minutes, 4 C) and viability was determined by trypan blue exclusion. Macrophages were resuspended at a final concentration of 1 × $10^6$ pMϕ/mL in Click's medium.

### *Antigen Presentation Assay*

For the antigen presentation assay, pMϕ were allowed to adhere onto 60-mm diameter plastic petri dishes at 37 C for 2 hours. Nonadherent cells were removed by repeated washing with Click's medium. The monolayer of pMϕ then was incubated for 20 minutes (37 C, 5% $CO_2$, in the dark) with 30 μg mitomycin C per milliliter (Sigma Chemical Co.). The plates were washed extensively with PBS, overlaid with 3 mL Click's medium plus 10% FBS (fetal bovine serum: Biologos Inc., Naperville, IL), and gently scraped off the surface using a rubber policeman. Cells were centrifuged, the viability determined, and pMϕ resuspended in Click's medium plus FBS. This protocol provided pMϕ cultures containing more than 95% macrophages, which were positive by nonspecific esterase staining and which demonstrated typical macrophage morphology. No difference in cell yields was observed between control and hemorrhaged mice. The capacity of pMϕ to present the specific antigen conalbumin was assessed by coculturing pMϕ with the mouse T-helper cell clone D10.G4.1 (ratio pMo:D10.G4.1 5000:20000 cells/well), as previously described by Ayala et al.[17] The D10.G4.1 cell clone (provided by Dr. Charles Janeway, New Haven, CT) proliferates in the presence of conalbumin presented by MHC class II antigen identical macrophages.[18] The degree of D10.G4.1 proliferation correlates with the capacity of pMϕ to present conalbumin.

### *Determination of MHC Class II Antigen Expression*

Major histocompatibility complex class II antigen (Ia) expression was determined as described by Ayala et al.[19] Macrophages were labeled with fluorescein-conjugated mouse $Ia^k$ alloantisera (Accurate Scientific, Westbury, NY). No fewer than 200 pMϕ were screened in each culture, recording both the number of fluorescent cells (Ia positive) and nonfluorescent cells. From these values, the percentage of Ia-positive cells were calculated.

### *Assessment of IL-1, IL-6, and TNF Production*

The capacity of mouse pMϕ to produce monokines (*i.e.*, IL-1, IL-6, and TNF-α) was determined by incubating 1 × $10^6$ pMϕ/mL/well in 24-well plates with 10 μg lipopolysaccharide (LPS, from *Escherichia coli* 055:B5, Difco Labs., Detroit, MI) per milliliter Click's medium with 10% FBS for 48 hours (37 C, 5% $CO_2$). The cell supernatants were collected at the end of the incubation period, filtered, aliquotted, and stored at −70 C until assayed.

The IL-1 activity in these cell cultures was determined by adding serial dilutions of the supernatant to the D10.G4.1 cells (2 × $10^4$ cells/well) in the presence of Concanavalin A (2.5 μg/mL; Pharmacia Fine Chemicals, Piscataway, NJ). Proliferation of the D10.G4.1 cells was measured with $^3$H thymidine incorporation.[17] Interleukin-6 was determined by the amount of proliferation of the murine hybridoma cell line 7TD1 (provided by Dr. Van Snick, Brussels, Belgium), which only grows in the presence of IL-6.[20] The 7TD1 cells (4 × $10^3$/well) stimulated with serial dilutions of the pMϕ supernatants were grown for 72 hours. At the end of the incubation period, MTT-tetrazolium (Sigma Chemical Co.) produced during the last 4 hours was measured photometrically. Similarly TNF activity was measured by assessing pMϕ supernatants for WEHI-164 clone 13 (provided by Dr. S. Kunkel, Ann Harbor, MI) cytotoxicity,[21] as described by Ayala et al.[17]

All samples were tested in triplicate. The relative unit(s) of monokine activity per milliliter were determined by comparison of the curves produced from the dilutions of the experimental supernatants to that generated by dilutions of a purified human IL-1 standard (5 U/mL; Genzyme Corp., Boston, MA), a recombinant human IL-6 standard (200 U/mL; Amgene Corp., Thousand Oaks, CA), or a murine TNF standard (200 U/mL; Amgene Corp.) according to the methods of Mizel.[22]

### *Determination of PGE$_2$ Plasma Levels*

Prostaglandin E$_2$ levels in plasma were measured with radioimmunoassay technique. Because contamination of the plasma by arachidonic acid was detected in preliminary measurements, PGE$_2$ in plasma was purified using a two-column extraction procedure under vacuum. Briefly, 200 to 300 μL plasma, acidified to pH 3.5 with 10 to 15 μL 2N HCl, were applied to a 100-mg Bond-Elut C18 column (Analytichem International, Harbor City, CA) that was prepared by washing with 1 mL methanol and 1 mL acidified water (pH 3.5). A 500-mg Bond-Elut Silica extraction column (Analytichem International) was washed with 5 mL benzene:ethyl acetate (80:20). After washing the PGE$_2$ bound to the C18 column with 2 mL each of acidified water, 15% methanol and petroleum ether, the PGE$_2$ was eluted with 1 mL ethyl acetate from the C18 column and bound to the silica column. The bound PGE$_2$ was washed with 1 mL each of benzene: ethyl acetate (80:20), benzene:ethyl acetate (60:40), benzene:ethyl acetate:methanol (60:40:2), and benzene:ethyl acetate:methanol (60:40:10). The PGE$_2$ was eluted from the silica column with 3 mL benzene:ethyl acetate:methanol (60:40:30) and dried under nitrogen at room temperature. The PGE$_2$ was reconstituted with assay buffer (0.9% NaCl, 0.01 mol/L ethylenediamine tetraacedic acid, 0.3% bovine gamma-globulin, 0.005% Triton X-100, 0,05% sodium azide, 25 mmol/L [millimolar] sodium phosphate buffer; pH 6.8). Plasma was assayed for PGE$_2$ using an $^{125}$I radioimmunoassay kit (NEN DuPont, Boston, MA) according to the manufacturer's directions. Samples were counted on a LKB 1282 Compugamma counter (LKB, Gaithersburg, MD). The concentrations of PGE$_2$ were determined by calculating B/Bo (net CPM of standard/net counts per minute (cpm) of '0' standard) and interpolation of a PGE$_2$ standard curve.

### *Statistics*

For statistical calculations unpaired Student's t test with Bonferroni correction was used. Values were considered significant if $p < 0.05$. Values are reported as mean ± standard error of the mean.

## Results

### *Antigen Presentation*

Antigen presentation by pMϕ obtained from hemorrhaged animals without ibuprofen treatment (12,337 ± 2061 cpm) revealed a significant ($p < 0.01$) suppression compared to sham-operated animals (30,190 ± 2252 cpm) (Fig. 1). However treatment with ibuprofen completely restored ($p < 0.05$) antigen presentation by pMϕ from hemorrhaged animals (35,938 ± 7305 cpm) to control values.

### *Ia Expression*

In parallel with antigen presentation, the capacity of pMϕ to express the MHC class II (Ia) antigen was markedly ($p < 0.01$) decreased in hemorrhaged animals (20.7%

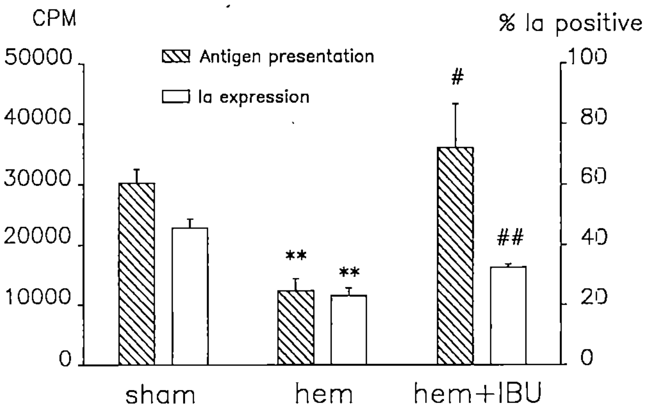

FIG. 1. Capacity of pMϕ to present the specific antigen conalbumin to the murine T-helper cell clone D10.G4.1 [CPM] and to express MHC class II (Ia) antigen [%Ia positive pMϕ] 24 hours after hemorrhage. Hemorrhaged saline-treated mice (hem; n = 6) were compared to sham-operated animals (sham; n = 6) and hemorrhaged animals with ibuprofen treatment (1 mg/kg BW; hem + IBU; n = 6). The data are presented as the mean ± SEM. **$p \leq 0.01$ hem *versus* sham; #$p \leq 0.05$/##$p \leq 0.01$ hem *versus* hem + IBU.

± 2.7% Ia positive cells) by 60% compared to sham animals (51.5% ± 3.0%) (Fig. 1). Administration of ibuprofen significantly ($p < 0.01$) improved $pM\phi$ capability to present Ia by 58% (32.7% ± 1.1%) when compared to the vehicle-treated group (20.7% ± 2.7%). Nonetheless a complete restoration of Ia expression was not observed after ibuprofen treatment.

### *Interleukin-1 Synthesis*

Interleukin-1 synthesis by $pM\phi$ from the vehicle-treated hemorrhaged group (4.15 ± 1.10 U/mL) was significantly ($p < 0.05$) decreased compared to sham-operated animals (11.6 ± 1.97 U/mL) (Fig. 2). Macrophages from ibuprofen-treated hemorrhaged animals demonstrated a high, but not significant, increase in IL-1 production of 108% (8.64 ± 1.73 U/mL) compared to the vehicle-treated group.

### *Interleukin-6 Synthesis*

Interleukin-6 production by $pM\phi$ from hemorrhaged mice (310 ± 6 U/mL) was reduced by 47% when compared to sham animals (589 ± 102 U/mL) (Fig. 2). Administration of ibuprofen immediately after hemorrhage resulted in a further decrease of IL-6 production by $pM\phi$ (184 ± 26 U/mL), which was statistically different ($p < 0.01$) from sham- and vehicle-treated animals.

### *Tumor Necrosis Factor-α Synthesis*

Twenty-four hours after hemorrhage and resuscitation, no significant difference in TNF production by $pM\phi$ from hemorrhaged animals (0.44 ± 0.18 U/mL) and sham-operated animals (0.60 ± 0.12 U/mL) was observed (Fig. 3). However ibuprofen treatment significantly ($p < 0.05$) increased TNF production by 239% (1.49 ± 0.27 U/mL) compared to the vehicle-treated group and by 148% compared to sham-operated animals.

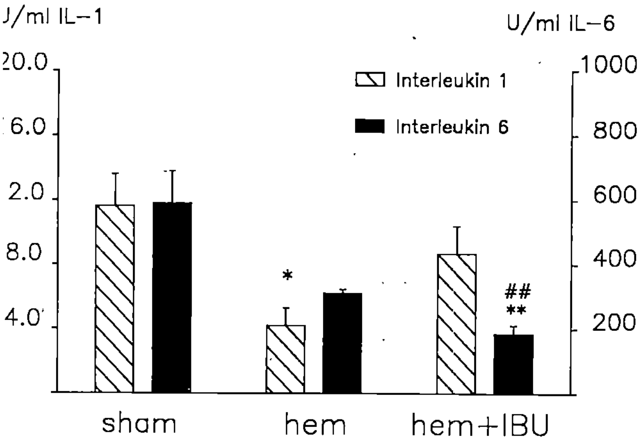

FIG. 2. Production of interleukin-1 [U/mL] and interleukin-6 [U/mL] from $pM\phi$ 24 hours after hemorrhage. Hemorrhaged saline-treated mice (n = 6) were compared to sham-operated animals (n = 6) and hemorrhaged animals with ibuprofen treatment (1 mg/kg BW; n = 6). Cytokine levels in supernatants were determined using specific bioassays (D10.G4.1 for IL-1, 7TD1 for IL-6). The data are presented as the mean ± SEM. $p \leq 0.05$/**$p \leq 0.01$ hem *versus* sham; ##$p \leq 0.01$ hem *versus* hem + IBU.

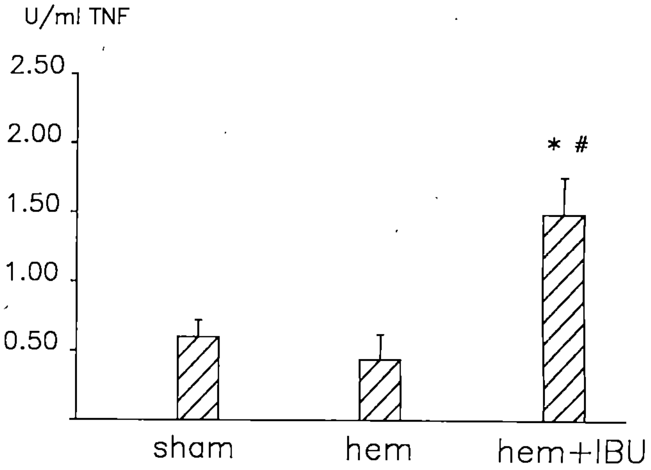

FIG. 3. Production of tumor necrosis factor α (cachectin) [U/mL] from $pM\phi$ 24 hours after hemorrhage. Hemorrhaged saline-treated animals (n = 6) were compared to sham-operated animals (n = 6) and hemorrhaged animals with ibuprofen treatment (1 mg/kg BW; n = 6). The WEHI 164 clone 13 cell line was used for TNF measurements in $pM\phi$ supernatants. The data are presented as the mean ± SEM. *$p \leq 0.05$ sham *versus* hem + IBU. #$p \leq 0.05$ hem *versus* hem + IBU.

### *Prostaglandin $E_2$ Plasma Levels*

Plasma levels of $PGE_2$ were significantly increased by 156% in hemorrhaged animals (63.7 ± 8.2 pg/mL) compared to the shams (24.9 ± 5.8 pg/mL) (Fig. 4). Plasma levels of $PGE_2$ from ibuprofen-treated animals (23.1 ± 12.8 pg/mL) demonstrated a massive reduction by 64% and the values were comparable to the shams (Fig. 4).

## Discussion

Our data demonstrate that increased $PGE_2$ plasma levels following hemorrhage correlated with the depressed macrophage antigen presentation, Ia expression, and IL-1 synthesis. Ibuprofen, a cyclooxygenase inhibitor, prevented the hemorrhage-induced suppression of peritoneal macrophage functions, despite a significant increase in cachectin synthesis.

Clinical studies showed a 10-fold increase of $PGE_2$ production by blood macrophages up to 21 days after major trauma.[23] In addition elevated serum levels of $PGE_2$ after burn injury in humans have been reported.[24] Furthermore experimental studies demonstrated that blockade of prostaglandin synthesis after burn injury in mice improved the depressed IL-2 synthesis[25] *in vitro*. These results from animal and clinical experiments, therefore, support the notion that $PGE_2$ *in vitro* is capable of suppressing dif-

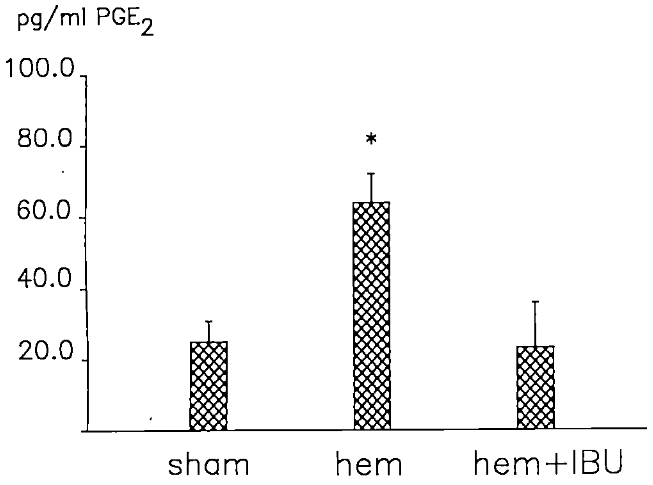

FIG. 4. Plasma levels of $PGE_2$ [pg/mL] 24 hours after hemorrhage. Hemorrhaged saline-treated animals (n = 3) were compared to sham-operated animals (n = 3) and hemorrhaged animals with ibuprofen treatment (1 mg/kg BW; n = 3). $PGE_2$ levels were determined with radioimmunoassay technique. The data are presented as the mean ± SEM. $^*p \leq 0.05$ hem *versus* sham.

ferent immune responses such as IL-1[26,27] and TNF[14] production, MHC class II antigen expression,[28] antigen presentation,[29] lymphokine synthesis by T lymphocytes[30] or B-lymphocyte proliferation,[31] and immunoglobulin production.[10]

Although we demonstrated in previous studies that simple hemorrhage caused a marked depression of the immune responses and macrophage functions,[1,4] it remained unknown whether increased $PGE_2$ synthesis by macrophages played any major role in inducing the observed immunosuppression and enhanced susceptibility to sepsis. This was investigated in this study by measurement of $PGE_2$ plasma levels as well as *via* administration of the cyclooxygenase inhibitor ibuprofen immediately after hemorrhage and resuscitation. Such studies were performed 24 hours after hemorrhage because recent findings revealed a significant suppression of various immune functions at this time point.[4,6,17] The dose of 1 mg ibuprofen per kilogram body weight used in this study is similar to that used in previous studies.[12,32]

Our data demonstrate that even simple hemorrhage without significant tissue trauma caused a significant elevation of plasma $PGE_2$ levels. Furthermore the observed suppression of antigen presentation capacity, Ia expression, and IL-1 synthesis correlated well with increased $PGE_2$ plasma levels. Thus it appears that there is a close relationship between elevated $PGE_2$ levels and decreased macrophage functions. This suggestion is supported by our studies that demonstrated that *in vivo* blockade of $PGE_2$ synthesis with ibuprofen significantly improved the depressed macrophage functions. This finding further confirms the immunosuppressive role of $PGE_2$ after hemorrhage. The observed immunoprotective effects of ibuprofen are in line with previous findings concerning the beneficial effect of cyclooxygenase inhibitors in the therapy of depressed cellular immune functions following burn injury in mice[32] and major surgery in humans.[12] However none of these studies investigated the effect of cyclooxygenase inhibitors on macrophage functions such as antigen presentation and monokine production. The enhancement of depressed macrophage functions such as antigen presentation and MHC class II antigen expression are important because macrophages play a key role in eliciting an adequate cellular and humoral immune response to microorganisms.

Whether enhanced cachectin production by Kupffer cells[33] correlating with elevated TNF plasma levels is responsible for the observed immunosuppression is so far not understood. Nonetheless it is known that very high levels of cachectin, as found during endotoxemia and sepsis, cause hypotension, cachexia, and increased mortality.[34,35] In addition blockade of TNF activity by monoclonal antibodies decreased rates of mortality after endotoxemia.[36] Our data show that blockade of $PGE_2$ synthesis with ibuprofen resulted in significantly increased TNF production. Therefore $PGE_2$ may be a major down-regulating agent for TNF synthesis not only *in vitro*, as shown by Kunkel et al.,[14] but also *in vivo*. The improvement of macrophage functions despite an elevated TNF production by macrophages following ibuprofen treatment further indicates that TNF, at least in amounts present during and after hemorrhage, does not have any immunosuppressive effect. In fact, TNF-$\alpha$ may even have a stimulatory effect on cellular immune responses as it is shown in several *in vitro* studies, where TNF-enhanced Fc receptor expression,[37] B-cell proliferation and differentiation,[38] T-lymphocyte growth,[39] as well as macrophage Ia expression.[40] Therefore it can be hypothesized from our data that a certain amount of TNF is necessary to activate immune and nonimmune cells, initiate, support, and maintain inflammatory responses following tissue injury induced by hemorrhage. In contrast overproduction of this monokine, as observed during sepsis,[41] or TNF-$\alpha$ infusion in high amounts[16,35] are detrimental for the host. Therefore TNF-$\alpha$ and cachectin might be the two different sides of the same biologic coin.

Although many studies concerning TNF-$\alpha$ and its effects have been carried out, little is known about the role and regulation of IL-6 production following hemorrhage and resuscitation. Studies from Guo et al.[42] and Waage et al.[43] demonstrated a significant correlation between endotoxemia, mortality after sepsis, and the degree of increased IL-6 levels in plasma. Whether increased IL-6 production only represents an important parameter in severe inflammation and infection or whether IL-6 is involved directly in the induction of immunosuppression is not known. In previous studies we demonstrated a peak of IL-6 plasma levels 2 hours after hemorrhage[13] and a significant increase of IL-6 synthesis by peritoneal macrophages (unpublished data). However 24 hours after hemorrhage the production of IL-6 from peritoneal macrophages was decreased compared to sham animals. Treatment with ibuprofen further decreased IL-6 synthesis. Whether this represents a direct effect of the anti-inflammatory agent ibuprofen on IL-6 synthesis or an indirect effect by blocking the production of other mediators that induce IL-6 synthesis remains unknown. The decreased IL-6 synthesis in ibuprofen-treated hemorrhaged animals correlated well with the increased production of IL-1 and TNF-$\alpha$. These data confirm the observations of Schindler et al.,[44] who described a suppressive effect of IL-6 on IL-1 and TNF-$\alpha$ synthesis by peripheral blood cells and indicate a potential down-regulating function of IL-6 after hemorrhage. Nonetheless the role of altered IL-6 production after hemorrhage must be investigated further.

In summary our data demonstrate that arachidonic acid metabolites such as $PGE_2$ but not cachectin are directly involved in the suppression of different macrophage functions after hemorrhage. *In vivo* blockade of $PGE_2$ production by ibuprofen following hemorrhage significantly improved macrophage functions and did not affect the hemodynamic response to resuscitation. Therefore the cyclooxygenase inhibitor ibuprofen represents a safe and potent agent in the therapy of hemorrhage-induced immunosuppression.

## References

1. Stephan RN, Ayala A, Harkema JM, et al. Mechanism of immunosuppression following hemorrhage: defective antigen presentation by macrophages. J Surg Res 1989; 46:553–556.
2. Stephan RN, Conrad PJ, Janeway CA, et al. Decreased interleukin-2 production following simple hemorrhage. Surg Forum 1986; 37:73–75.
3. Abraham E, Freitas AA. Hemorrhage in mice induces alterations in immunoglobulin-secreting B cells. Crit Care Med 1989; 17: 1015–1019.
4. Ayala A, Perrin MM, Chaudry IH. Defective macrophage antigen presentation following hemorrhage is associated with the loss of MHC class II (Ia) antigens. Immunology 1990; 70:33–39.
5. Ertel W, Morrison MH, Ayala A, et al. Interferon-$\gamma$ (IFN-$\gamma$) administration *in vivo* following hemorrhagic shock restores macrophage (M$\phi$) antigen presentation and the processes with it. Circ Shock 1990; 31:30.
6. Stephan RN, Kupper TS, Geha AS, et al. Hemorrhage without tissue trauma produces immunosuppression and enhances susceptibility to sepsis. Surgery 1987; 122:62–68.
7. Faist E, Mewes A, Baker CC, et al. Prostaglandin $E_2$ ($PGE_2$)-dependent suppression of interleukin-2 (IL-2) production in patients with major trauma. J Trauma 1987; 27:837–848.
8. Miller-Graziano CL, Fink M, Yan Wu J, et al. Mechanisms of altered monocyte prostaglandin $E_2$ production in severely injured patients. Arch Surg 1988; 123:293–299.
9. Walker C, Kristensen F, Bettens F, DeWeck AL. Lymphokine regulation of activated ($G_1$) lymphocytes: prostaglandin $E_2$-induced inhibition of interleukin 2 production. J Immunol 1983; 130: 1770–1773.
10. Knapp W, Baumgartner G. Monocyte-mediated suppression of human B lymphocyte differentiation in vitro. J Immunol 1978; 121:1177–1183.
11. Ertel W, Faist E, Salmen B, et al. Influence of cyclooxygenase inhibition on interleukin-2 receptor (IL-2R) expression after major trauma. Surg Res Comm 1989: 5:17–23.
12. Faist E, Ertel W, Cohnert T, et al. Immunoprotective effects of cyclooxygenase inhibition in patients with major surgical trauma. J Trauma 1990; 30:8–18.
13. Ayala A, Perrin MM, Meldrum DR, et al. Hemorrhage induces an increase in serum TNF which is not associated with increased levels of endotoxin. Cytokine 1990; 2:170–174.
14. Kunkel SL, Spengler M, May MA, et al. Prostaglandin $E_2$ regulates macrophage-derived tumor necrosis factor gene expression. J Biol Chem 1988; 263:5380–5384.
15. Sheppard BC, Fraker DL, Norton JA. Prevention and treatment of endotoxin and sepsis lethality with recombinant human tumor necrosis factor. Surgery 1989; 106:156–162.
16. Tracey KJ, Beutler B, Lowry SF, et al. Shock and tissue injury induced by recombinant human cachectin. Science 1986; 234:470–474.
17. Ayala A, Perrin MM, Wagner Ma, Chaudry IH. Enhanced susceptibility to sepsis after simple hemorrhage: depression of Fc and C3b receptor mediated phagocytosis. Arch Surg 1990; 125:70–75.
18. Kaye J, Procelli S, Tite J, et al. Both monoclonal antibody and antisera specific for determinants unique to individual cloned helper T cell lines can substitute for antigen in the activation of T cells. J Exp Med 1983; 158:836–856.
19. Ayala A, Kierszenbaum F. The effects of p-chloromercuri-phenylsulfonic acid on Trypanosoma cruzi infection of mammalian host cells in vitro. Mol Biochem Parasitol 1987; 23:63–69.
20. Van Snick J, Cayphas S, Vink A, et al. Purification and $NH_2$-terminal amino acid sequence of a T-cell-derived lymphokine with growth factor activity for B-cell hybridomas. Proc Natl Acad Sci USA 1989; 83:9679–9683.
21. Espevik T, Nissen-Meyer J. A highly sensitive cell line, WEHI 164 clone 13, for measuring cytotoxic factor/tumor necrosis factor from human monocytes. J Immunol Methods 1986; 95:99–105.
22. Mizel SB. Production and quantitation of lymphocyte activating factor (interleukin 1). *In* Herscowitz HB, Holden HT, Bellanti JA, Ghaffar A, eds. Manual of Macrophage Methodology. New York: Marcel Dekker, 1981, pp 407–416.
23. Faist E, Mewes A, Strasser T. Alterations of monocyte function following major injury. Arch Surg 1988; 123:287–292.
24. Ninnemann JL, Stockland AE. Participation of prostaglandin E in immunosuppression following thermal injury. J Trauma 1984; 24:201–207.
25. Wood JJ, Grbic JT, Rodrick ML, et al. Suppression of interleukin 2 production in an animal model of thermal injury is related to prostaglandin synthesis. Arch Surg 1987; 122:179–184.
26. Kunkel SL, Chensue SW, Phan SH. Prostaglandins as endogenous mediators of interleukin-1 production. J Immunol 1986; 136: 186–192.
27. Knudsen PJ, Dinarello CA, Strom TB. Prostaglandins post-transcriptionally inhibit monocyte expression of interleukin-1 activity by increasing intracellular cyclic adenosine monophosphate. J Immunol 1986; 137:3189–3194.
28. Zlotnik A, Shimonkevitz R, Kappler J, Marrack P. Effect of prostaglandin $E_2$ on the $\Gamma$-interferon induction of antigen presenting ability in P388D1 cells and on IL-2 production by T-cell hybridomas. Cell Immunol 1985; 90:154–166.
29. Stephan RN, Conrad PJ, Saizawa M, et al. Prostaglandin $E_2$ depresses antigen-presenting cell function of peritoneal macrophages. J Surg Res 1988; 44:733–739.
30. Rappaport RS, Dodge GR. Prostaglandin E inhibits the production of human interleukin 2. J Exp Med 1982; 155:943–948.
31. Simkin N, Jelinek DF, Lipsky PE. Inhibition of human B cell responsiveness by prostaglandin $E_2$. J Immunol 1987; 138:1074–1081.

32. Hansbrough J, Peterson V, Zapata-Sirvent R, Claman HN. Postburn immunosuppression in an animal model. II. Restoration of cell-mediated immunity by immunomodulating drugs. Surgery 1984; 95:290–296.
33. Ayala A, Perrin MM, Ertel W, Chaudry IH. The effects of hemorrhage on Kupffer cell antigen presentation (AP) and those processes associated with it. FASEB J 1990; 4:1020.
34. Beutler B, Cerami A. The biology of cachectin/TNF—A primary mediator of the host response. Ann Rev Immunol 1989; 7:625–655.
35. Tracey KJ, Kowrey SF, Fahey TS, et al. Cachectin/tumor necrosis factor induces lethal shock and stress hormone responses in the dog. Surg Gynecol Obstet 1987; 164:415–422.
36. Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science 1985; 229:869–871.
37. Hoffmann M, Weinberg JB. Tumor necrosis factor-alpha induces hydrogen peroxide production and Fc receptor expression, but not increased Ia antigen expression by peritoneal macrophages. J Leuc Biol 1987; 42:704–707.
38. Jelinek DF, Lipsky PE. Enhancement of human B-cell proliferation and differentiation by tumor necrosis factor-alpha and interleukin 1. J Immunol 1987; 139:2970–2976.
39. Zucali JR, Elfenbein GJ, Barth KC, Dinarello CA. Effects of human interleukin 1 and human tumor necrosis factor on human T lymphocyte colony formation. J Clin Invest 1987; 80:772–777.
40. Chang RJ, Lee SH. Effects of interferon-Γ and tumor necrosis factor-alpha on the expression of an Ia antigen on a murine macrophage cell line. J Immunol 1986. 137:2853–2856.
41. Waage A, Haltensen A, Espevik T. Association between tumor necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet 1987; i:355–357.
42. Guo Y, Wiener S, Winchurch RA, et al. Interleukin-6, a potent immunoregulatory cytokine in burn patient serum. Surg Forum 1989; 37:58–60.
43. Waage A, Bradtzaeg P, Halstensen A, et al. The complex pattern of cytokines in serum from patients with meningococcal septic shock. J Exp Med 1989; 169:333–338.
44. Schindler R, Mancilla J, Endres S, et al. Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. Blood 1990; 75:40–47.

# Simultaneous Bilateral Hernia Repair

## *A Case Against Conventional Wisdom*

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**The timing of bilateral hernia repair remains controversial. Because of reported high recurrence rates after simultaneous bilateral repair, staged procedures have been suggested. This study determined recurrence and complication rates of unilateral *versus* simultaneous bilateral repair. Of 659 patients undergoing hernia repair between 1974 and 1980, 333 underwent unilateral repair and 329 had simultaneous bilateral repair. More than 90% of patients were followed until death or a minimum of 60 months (median, 104 months). Perioperative complications were associated with 18% of repairs. More morbidity occurred in the bilateral group. However complication rates for specific events were not significantly different, except for urinary retention, which occurred in 20 patients (6.1%) of the unilateral group and 49 (15%) of the bilateral group ($p < 0.001$). Overall 25 recurrences occurred in the unilateral group and 31 in the bilateral group. Recurrence rates at 5 and 9 years were, respectively, 4.8% and 8.8% in the unilateral group and 5.0% and 9.1% in the bilateral group ($p = 0.861$). These data suggest that simultaneous bilateral inguinal herniorrhaphy does not result in increased rates of most postoperative complications or recurrence when compared with unilateral repair.**

INGUINAL HERNIA REPAIR is the most frequently performed abdominal operation. Approximately 500,000 hernia operations are performed yearly, an estimated 20% of which are for recurrent hernia. Bilateral hernias occur in about 12% of patients. Several authors have reported that the recurrence rate of bilateral hernia exceeds that of unilateral hernia. On the basis of this information, some surgeons have argued against simultaneous bilateral hernia repair.[1-5]

The purpose of this study was to determine whether he rate of hernia recurrence after unilateral repair is significantly different from that after bilateral repair, a factor hat might aid in determining the timing of bilateral hernia epair.

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## Materials and Methods

### *Study Group*

The charts of 1541 patients who underwent inguinal hernia repair at the Mayo Clinic between 1974 and 1980 were reviewed retrospectively. Exclusionary criteria included repair of recurrent hernia, preperitoneal repair, and age younger than 18 years. The charts were analyzed with regard to preoperative conditions considered to increase the chance of hernia recurrence, such as (1) constipation (defined as less than one bowel movement per 48 hours or a physician's note of this condition in the record); (2) a history of chronic obstructive pulmonary disease, documented by pulmonary function testing; (3) obesity, defined as more than 20% over ideal body weight; or (4) a history of prostatism, documented by cystoscopy. Additional items recorded included the age of the patient, type of hernia, the side of occurrence, complications associated with repair or hospitalization, and whether repair was performed by an attending surgeon or a member of the surgical house staff. Follow-up data were obtained during a return visit of the patient or by written or verbal correspondence.

### *Clinical Data*

Of the 1541 patients, 659 met the criteria of the study. The mean age of the 330 patients in the unilateral repair group was 59.5 years, and that of the 329 patients in the bilateral group was 61 years. Of the 330 patients who underwent unilateral repair, 294 were male and 36 (10.9%) were female, and of the 329 patients in the bilateral group, 309 were male and 20 (6.1%) were female. Before oper-

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ation 1.2% of the patients in the unilateral repair group had a documented history of constipation, 9.4% were reported to have chronic obstructive pulmonary disease, 26.7% were obese, and 15.3% of the male patients had prostatism. Of the patients who had bilateral hernia repair, 2.4% had evidence of constipation, 8.8% were obese, 10.0% had chronic obstructive pulmonary disease, and 17.5% of the male patients had prostatism. The differences between the unilateral and bilateral groups in regard to these factors were not statistically significant, except for the fact that patients undergoing unilateral hernia repair were more likely to be obese (26.7% *versus* 8.8%; $p < 0.001$) (Table 1).

The pertinent clinical data comparing the unilateral group with the bilateral group are shown in Table 1.

### *Statistical Analysis*

Comparison of hernia recurrence rates between the unilateral and the bilateral repair groups was based on survival analysis methodology with the time free of recurrence described with Kaplan–Meier methods and compared with the log rank test and Cox regression models. Patients who died, who were lost to follow-up, or who were followed to the end of observation (December 1988) without recurrence were considered censored. Assessment of postoperative complications was based on $\chi^2$ tests. Comparisons of age and hospital stay were based on the conventional Student t test.

## Results

Unilateral hernia repair was performed on 330 patients and simultaneous bilateral hernia repair was done on 329 patients.

TABLE 1. *Clinical Data for 659 Patients Who Had Inguinal Hernia Repair*

| | Type of Repair | |
|---|---|---|
| Factor | Unilateral | Bilateral |
| No. of patients in group | 330 | 329 |
| No. male/female | 294/36 | 309/20 |
| Mean age (years) | 59.5 | 61.0 |
| Preperative conditions | | |
| No. of patients | | |
| History of constipation | 4 | 8 |
| History of chronic obstructive pulmonary disease | 31 | 33 |
| History of obesity | 88 | 29 ($P = 0.001$) |
| History of prostatism | 45 | 54 |
| Mean duration of hospitalization (days) | 6.4 | 6.2 |
| (range) | (3–26) | (3–18) |

TABLE 2. *Analysis of Recurrence in 659 Patients Who Had Inguinal Hernia Repair*

| | Type of Repair* | |
|---|---|---|
| | Unilateral (n = 330) | Bilateral (n = 329) |
| Side | | |
| Right | 190 (15) | — |
| Left | 140 (10) | — |
| Type | | |
| Direct | 72 (4) | 119 (13) |
| Indirect | 204 (17) | 90 (8) |
| Components of both types | 54 (4) | 120 (10) |
| No. of recurrences | 25 | 31 |
| Recurrence rate (%) | | |
| 5-year | 4.8 | 5.0<br>($p = 0.861$) |
| 9-year | 8.8 | 9.1 |

* Number of recurrences shown in parentheses.

Staff surgeons operated on 469 (71.1%) of the patients, and surgical residents performed the repair in 190 (28.8%) patients.

### *Type of Hernia*

In the unilateral repair group, 57.5% of the hernias were right-sided. Indirect hernias occurred in 61.8% of patients, direct hernias were found in 21.8%, and elements of both hernia types were noted in 16.4%. The number of indirect hernias in the unilateral repair group was significantly higher ($p < 0.001$) than in the bilateral repair group. Among the patients who had bilateral hernia repair, 27.4% had indirect hernias, 36.2% had direct hernias, and 36.5% had hernias that contained direct and indirect components on one or both sides.

### *Anesthesia*

In the unilateral repair group, 286 patients (86.9%) had general anesthesia, 15 (4.6%) had local, and 28 (8.5%) had spinal. Of the patients who had bilateral repair, 312 (94.8%) had general anesthesia, none had local, and 17 (5.2%) had spinal.

### *Recurrence*

Hernia recurred in 56 patients. The recurrence rates at 5 and 9 years were 4.8% and 8.8%, respectively, in the unilateral repair group and 5.0% and 9.1%, respectively, in the bilateral hernia repair group ($p = 0.861$). After adjustment for differences between groups in the frequency of obesity, there was still no difference between groups ($p = 0.667$).

Recurrence rates also were analyzed with respect to the type and side of hernia at presentation (Table 2). The 5- and 9-year recurrence rates were 4.9% and 9.2% for right-sided hernias and 4.7% and 8.4% for left-sided hernias, respectively. Among the patients who underwent bilateral hernia repair, indirect hernia recurrence rates were 4.9% and 10.1% at 5 and 9 years, and for the direct hernias the 5- and 9-year recurrence rates were 5.5% and 7.3%. Hernias with direct and indirect components had recurrence rates of 4.7% and 7.1% at 5 and 9 years, respectively.

For the patients who had repair of unilateral indirect hernias, recurrence rates were 6.0% and 9.9% at 5 and 9 years, and for the direct hernias the rates at 5 and 9 years were 1.7% and 7.2%, respectively. Unilateral hernias with both direct and indirect components recurred at rates of 4.4% and 6.8% at 5 and 9 years, respectively. No statistically significant difference was demonstrated for recurrence of hernias of any side or type (Table 2).

Recurrence rates also were evaluated with regard to whether staff surgeons or senior house officers performed the hernia repair. The 5- and 9-year rates did not differ between the unilateral and bilateral repair groups (p > 0.10), regardless of the level of experience possessed by the operating surgeon (Table 3).

Consideration was given to recurrence rates as a function of preoperative conditions, level of experience of the operating surgeon, and perioperative complications. No statistically significant differences in the recurrence rates of hernia were noted between the unilateral and bilateral repair groups as a consequence of these factors (p > 0.10).

### Hospitalization

The mean duration of hospitalization was 6.4 days in the unilateral repair group and 6.2 days in the bilateral repair group. The difference was not statistically significant (Table 1).

TABLE 3. *Recurrence Rates and Morbidity in 659 Patients Who Had Inguinal Hernia Repair, by Level of Experience of Surgeon*

| Level of Experience | Type of Repair: Unilateral (n = 330) | | Bilateral (n = 329) | |
|---|---|---|---|---|
| | Recurrence Rate (%) | | | |
| | 5 yrs | 9 yrs | 5 yrs | 9 yrs |
| taff | 4.6 | 8.9 | 4.9 | 8.9 |
| ouse officer | 5.5 | 9.0 | 3.3 | 10.0 |
| value | 0.745 | | 0.827 | |
| | Complication Rate* | | | |
| taff | 24/248, 9.6% | | 51/221, 23% | |
| ouse officer | 14/82, 17% | | 28/108, 26% | |
| value | 0.069 | | 0.570 | |

* Numerator is the number of patients with complications, and deominator is the total number of patients who had repair.

TABLE 4. *Complications in 659 Patients Who Had Inguinal Hernia Repair*

| Complication | Type of Repair, No. of Patients: Unilateral (n = 330) | Bilateral (n = 329) |
|---|---|---|
| Operative death | 0 | 1 |
| Wound infection | 3 | 6 |
| Scrotal hematoma | 9 | 13 |
| Urinary retention | 20 | 49* |
| Urinary tract infection | 5 | 11 |
| Pulmonary embolus | 1 | 1 |
| Myocardial infarction | 0 | 0 |
| Cardiac arrhythmia | 4 | 2 |
| Ileus | 0 | 4 |
| Deep vein thrombosis | 1 | 1 |
| Total no. of complications | 43 | 88* |
| Total no. of patients with complications | 38 | 79* |

* Statistically significant difference between groups (p < 0.001).

### Morbidity

Overall postoperative complications occurred in 38 (11.5%) of the patients in the unilateral repair group and in 79 (24.0%) of the patients in the bilateral repair group (p < 0.001) (Table 4). Morbidity also was analyzed with respect to the level of experience of the operating surgeon. The postoperative course of patients who had hernia repair performed by staff surgeons was complicated in 24 (9.6%) of the patients in the unilateral group and in 51 (23%) of the patients in the bilateral group. Of the patients who had hernia repair performed by the surgical house staff, postoperative complications occurred in 14 (17%) (p = 0.069) in the unilateral group and in 28 (26%) in the bilateral group (p = 0.570) (Table 3).

Of the 659 patients studied, one died. This patient, who had a history of significant chronic obstructive pulmonary disease, underwent bilateral repair and suffered a fatal pulmonary embolism on the fifth postoperative day. A total of nine wound infections (three in the unilateral group and six in the bilateral group) occurred; infection was defined either as the expression of purulent material or as a wound requiring incision and drainage with or without administration of antibiotics. Nine scrotal hematomas occurred in the unilateral group, and 13 were found in the bilateral repair group. Urinary retention occurred in 20 patients who had unilateral repair and in 49 patients who had bilateral repair. Urinary tract infection (defined as more than 100,000 bacteria colony-forming units per milliliter in a urine specimen) occurred in five patients in the unilateral group and 11 patients in the bilateral group. Pulmonary emboli occurred in two patients, one in each group. Major arrhythmias requiring medical or electric therapy occurred in four patients in the unilateral group and two patients in the bilateral group.

Ileus requiring nasogastric intubation occurred in four patients, all in the bilateral repair group. The small number of occurrences makes suppositions of significance tenuous at best. Two deep venous thrombi developed, in one patient of each group.

## Discussion

The results of this retrospective review suggest that the recurrence rate after simultaneous bilateral hernia repair is not higher than that after unilateral hernia repair. Overall recurrence rates of approximately 5% and 9% at 5 and 9 years are consistent with the data reported elsewhere.[4–7] The average hospital stay was not increased after bilateral repair, although in both groups it was longer than present-day hospitalization, which typically ranges from outpatient care to 48 hours. Both the influence of third-party payers and the high incidence of concurrent and consecutive operative procedures unrelated to hernia repair performed on these patients explain this discrepancy.

Although the type of repair and the individual surgeon performing the operation were not considered in this study, there is no reason to believe that the two groups should differ in these areas because of the relative uniformity of surgical philosophy and ability at our institution. Limitations of this study include the desirability of a 10-year follow-up (the median duration of follow-up in this series was 104 months) and the use of written questionnaires.[8] Although these issues may be valid, they should affect both groups similarly (that is, one would expect an equivalent number of patients in both the unilateral and the bilateral repair groups to be unaware of their recurrent hernias).

The cause of hernia recurrence has been blamed on tension at the suture line by many authors.[4,7,9] The corollary to this supposition is that simultaneous repair creates tension at both repair sites. As proponents of one-stage hernia repair note, this finding has not been documented by autopsy studies.[10]

Despite a lack of anatomic evidence incriminating simultaneous bilateral hernia repair as causing bilateral suture line tension, a major surgical text notes, 'Most surgeons feel that in adults it is better to stage these [bilateral hernia] operations, rather than doing both simultaneously. The recurrence rate when bilateral repairs are done simultaneously in adults seems unacceptably high.'[1] An article cited in this text, and in many other sources, that reports an increased recurrence rate in bilateral repair is that by Palumbo and Sharpe in 1971.[3] In that remarkable report of 3572 primary inguinal hernioplasties in 3155 patients, the authors report only 37 recurrences, 75% of which occurred after the third postoperative year. They note that 2 recurrences occurred among 78 simultaneous bilateral repairs (2.5%), whereas only 4 recurrences were found among 756 staged bilateral repairs (0.5%). Although many surgeons offer this reference as justification for performing interval bilateral hernia repair, the authors clearly state that they have performed simultaneous repair for the past 10 years.

The benefits of simultaneous repair are obvious and have been discussed formally by Palumbo and Sharpe,[3] and more recently by others who reported no increased morbidity or recurrence in a single-stage bilateral repair.[10,11] These advantages include minimization of anesthesia and operating time, financial savings, more efficient use of hospital beds, and avoidance of the risk of strangulation or incarceration of the opposite side during the interval between staged operations.

Although in our study the total number of complications was statistically greater in the bilateral group than in the unilateral group, urinary retention was the only complication that occurred significantly more often in the bilateral group than in the unilateral group. This finding could not be explained as a consequence of patients with prostatism, despite the fact that more patients with prostatism were in the bilateral group. The clinical significance of this finding is questionable. In all cases urinary retention was a transient process relieved by urinary catheter placement, and it was not associated with an increased incidence of urinary tract infection or hernia recurrence. In all likelihood urinary retention was related to a greater degree of peripelvic tissue manipulation than in the unilateral repair and to secondary spasm of genitourinary musculature.

Of primary importance was the fact that none of the preoperative conditions, patient sex, or type or side of the hernias was statistically related to an increased rate of hernia recurrence. In addition recurrence rates were not statistically affected by the level of training of the operating surgeon. There is some evidence, although not statistically significant ($p = 0.069$), of a difference in complication rates in the unilateral group when repair performed by house officers was compared with repair by staff surgeons, but the small absolute number of morbid events in this group makes suppositions of cause meaningless.

Although it has been about 100 years since the introduction of modern hernia repair by Bassini and Marcy, surgeons have failed to reach a consensus regarding the timing of bilateral hernia repair.[12,13] Proponents of staged hernia repair have held that a higher recurrence rate is associated with simultaneous repair. Our results comparing more than 300 patients who had simultaneous bilateral repair with a virtually equal number of patients who had unilateral repair failed to demonstrate a statistically significant increase in either recurrence rate or rate of perioperative complications, except for that of transient urinary retention. This finding may aid the surgeon in the decision-making process when faced with patients requiring bilateral inguinal hernia repair.

## References

1. Morton JH. Abdominal wall hernias. *In* Schwartz SI, Shires GT, Spencer FC, eds. Principles of Surgery. New York: McGraw-Hill Book Co., 1989, p 1540.
2. Wantz GE. Complications of inguinal hernial repair. Surg Clin North Am 1984; 64:287–298.
3. Palumbo LT, Sharpe WS. Primary inguinal hernioplasty in the adult. Surg Clin North Am 1971; 51:1293–1307.
4. Nyhus LM, Condon RE. Hernia, 2nd Edition. Philadelphia: JB Lippincott, 1978.
5. Cahlin E, Weiss L. Results of postoperative clinical examination of inguinal hernia after three years. Acta Chir Scand 1980; 146: 421–426.
6. Ingimarsson O, Spak I. Inguinal and femoral hernias: long-term results in a community hospital. Acta Chir Scand 1983; 149:291–297.
7. Lichtenstein IL, Shulman AG, Amid PK, Montllor MM. The tension-free hernioplasty. Am J Surg 1989; 157:188–193.
8. Abrahamson JH, Gofin J, Hopp C, Makler A. The epidemiology of inguinal hernia: a survey in western Jerusalem. J Epidemiol Community Health 1978; 32:59–67.
9. Postlethwait RW. Recurrent inguinal hernia. Ann Surg 1985; 202: 777–779.
10. Ger R, Omar AM, Moza SK. Bilateral adult inguinal hernia. One-stage or two-stage operation? J R Coll Surg Edinb 1978; 23:300–302.
11. Duvie SO. One-stage bilateral inguinal herniorrhaphy in the adult. Can J Surg 1984; 27:192–193.
12. Bassini E. Ueber die Behandlung des Leistenbruches. Arch Klin Chir 1890; 40:429–476.
13. Marcy HO. The cure of hernia by the antiseptic use of animal ligature. *In* Cormac WM, Makins GH, eds. Transactions of the International Medical Congress, 7th Session. London: JW Kolckmann, 1881, pp 446–447.

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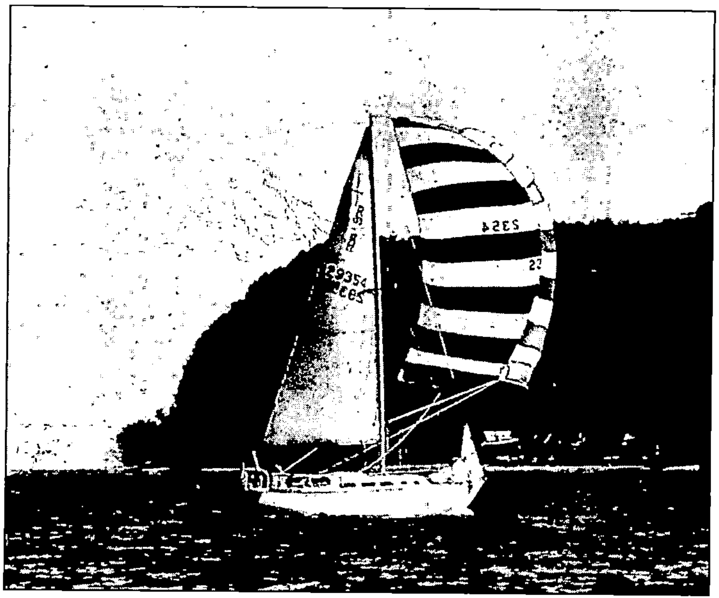

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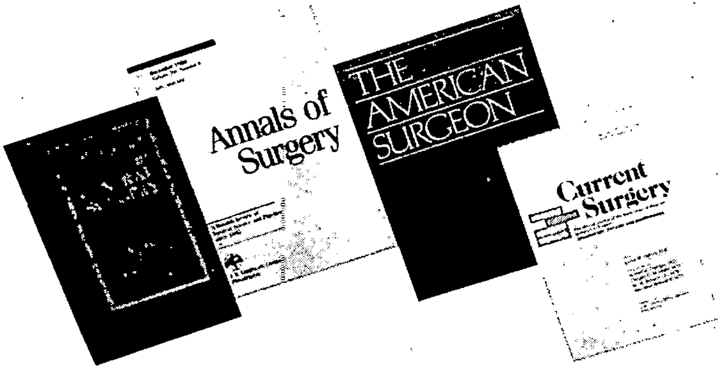

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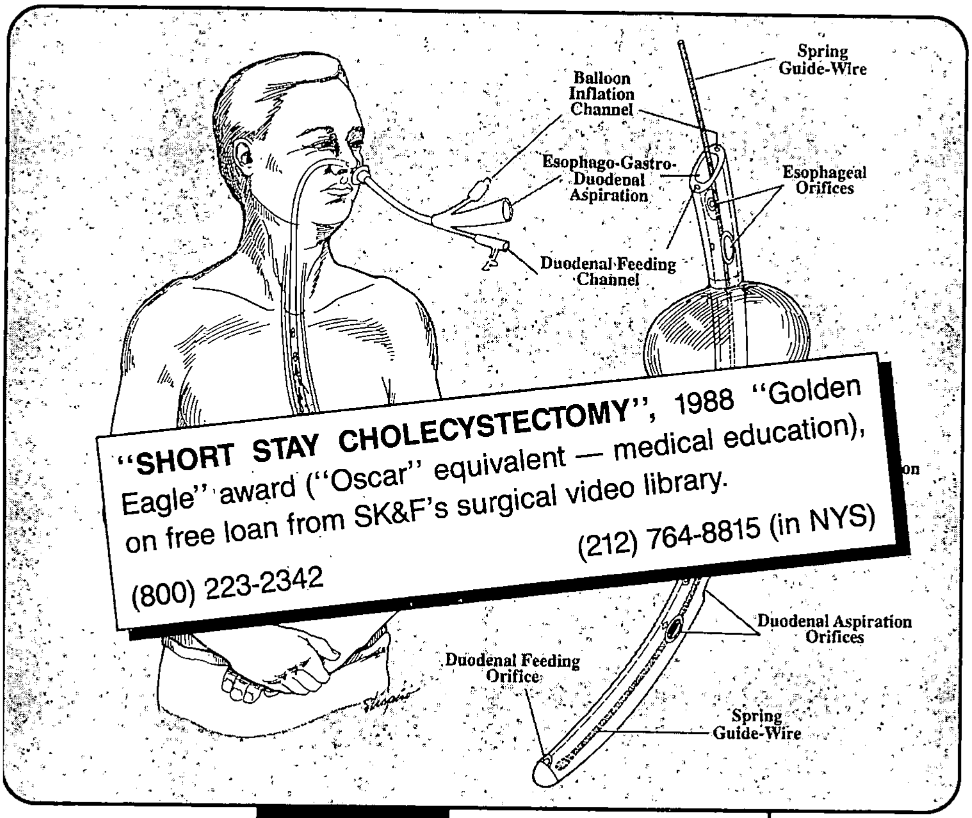

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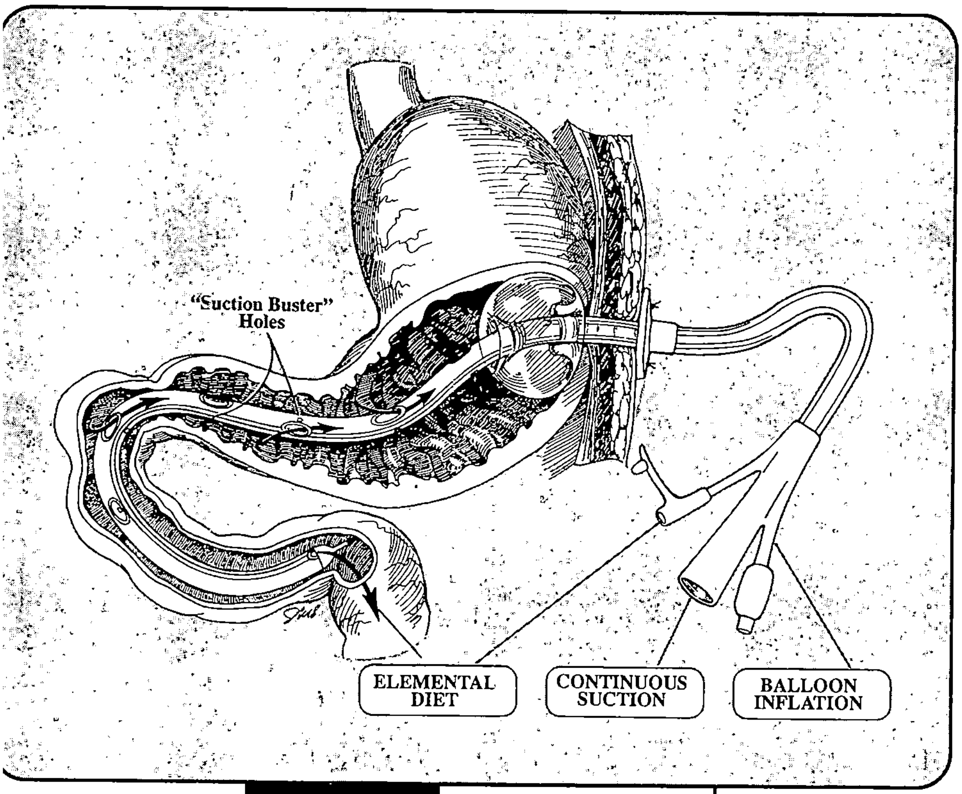
Esophageal/duodenal decompression is 12-14 times more efficient than gastric aspiration of alternative devices.* "Enteral hyperalimentation" begins immediately postop, with reported decreased sepsis, wound problems and markedly shortened L.O.S.*



**Moss**® Gastrostomy Tube

© Gerald Moss, PhD, MD, FACS

Patented

**Moss**®

Decompression--
Feeding Catheters

Mark IV is the most compact (#18 French), efficient, and occlusion resistant design since initially introduced in 1963. Its integral spring guide-wire makes it the most easily passed.

Distributed By:

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12196
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Made of #18 French biocompatable silicone for minimum trauma without sacrificing efficiency of performance.

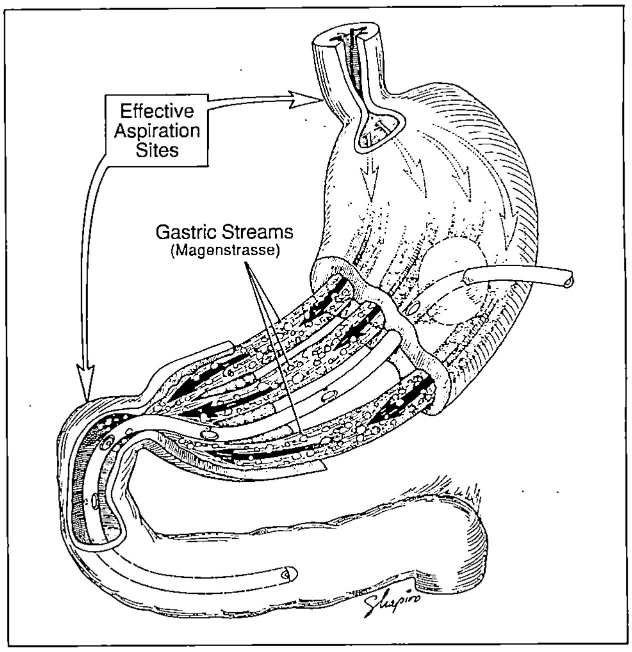
* Send for reprints documenting results from independent clinical centers.

# INCOMPARABLE MOSS®TUBES ....

## (but compare with other feeding-decompression tubes anyway.)

### 1. Decompression Site

**Gastric** suction alone cannot work! The stomach's longitudinal folds mimic parallel segments of intestine. Aspiration orifices may empty a single "Magenstrasse" (figure A). Most swallowed air avoids suction, and is propelled through the pylorus via adjacent channels. A clinical study of other N-G and G-tubes measured 32-42% inefficiency. *A toll booth in the center of a wide highway cannot collect from traffic in the outer lanes.*
Removal of air is most effective at constricted (single-file) sites. Measured efficiency increases 12-fold by adding aspiration within the adjacent esophagus and/or duodenum. And flowing duodenal digestive juices "self-cleanse" the tube of occluding mucus.

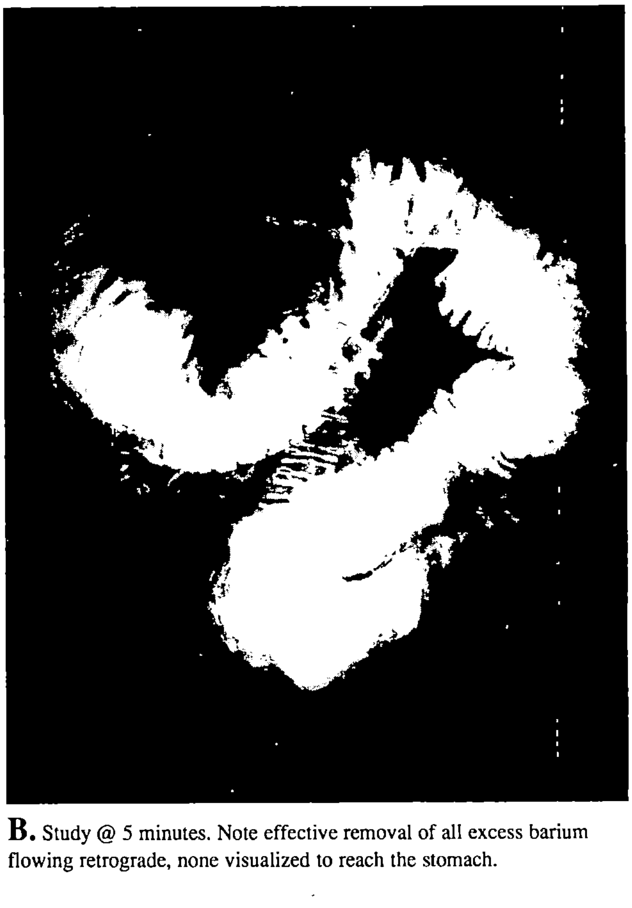


**A.** The functioning stomach subdivides into discrete"Magenstrasse". Any tube can only evacuate the single gastric stream within which it lies.

### 2. Feeding site

**Gastric** feeding risks distention and aspiration. **Jejunal** delivery bypasses 1-3 feet of proximal intestine, acting as a barrier to retrograde decompression. Aspiration of feedings is less likely, but remains a risk. Minimal initial infusion (starvation) is manditory initially.

The **Moss®G-Tube's duodenal** delivery site is the most effective. With proximal duodenal aspiration (patented), the initial distal feeding rate is unlimited. Clinical x-rays visualized removal of all excess feeding, with none reaching the stomach. (Fig. B) The full length of intestinal bsorption is available immediately. Earliest "enteral yperalimentation" is safely instituted within the recovery oom. Positive nutritional balances are achieved, leading o enhanced sepsis resistance, accelerated wound healing nd shorter L.O.S.



**B.** Study @ 5 minutes. Note effective removal of all excess barium flowing retrograde, none visualized to reach the stomach.

### 3. Aspiration Orifices

Uniformly sized orifices (**all others**) "suck in" mucosa to occlude the openings and stop decompression. Mucosal release then requires a null period (intermittant suction). Prograde air or retrograde feedings can be propelled accross and beyond the stomach, causing distention or aspiration.

By pairing each large orifice with a patented, smaller suction buster"®opening (**Moss®G-tube**), continuous spiration is maintained despite inadvertantly elevated uction.

### 4. Biomaterials

The **Moss®G-Tube** is **all silicone**, the accepted "gold standard" for optimum long term stability, tissue tolerance nd biocompatibility.

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